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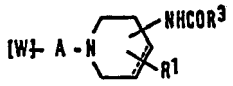
(54) AMINO- AND ACYLAMINO-PYRIDINE AND -HYDROPYRIDINE DERIVATIVES

(71) We, JOHN WYETH & BROTHER LIMITED, of Huntercombe Lane South, Taplow, Maidenhead, Berkshire, a British Company, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to pharmaceutical compositions containing heterocyclic compounds, to the novel compounds contained in these compositions and processes for their manufacture.

One aspect of the present invention is the provision of a pharmaceutical composition comprising a heterocyclic compound of the general formula



I(a)

in which the dotted line represents an optional double bond; W represents a cycloalkyl radical containing five to seven ring carbon atoms or an aryl or heteroaryl radical other than an indolyl radical, all of which radicals may be substituted or unsubstituted; A represents a lower-alkylene radical, a mono- or diketo lower-alkylene radical or an

oxime, aminoguanidone or substituted or unsubstituted hydrazone derivative thereof, a hydroxy-lower-alkylene radical, or a bivalent radical of the formula

$$-NH.CO.(CH_2)_n-,$$

$$-N(\text{Acyl}).CH_2.C\equiv C.CH_2-,$$

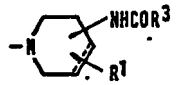
$$-O-CH_2.CH(OH).CH_2-$$

or

$$-O-(\text{lower-alkylene})-;$$

R^1 represents hydrogen, halogen or lower alkyl; R^3 represents a substituted or unsubstituted aryl radical (including heteroaryl radicals), aryl-lower-alkyl, diaryl-lower alkyl, cycloalkyl containing from five to seven ring carbon atoms, lower alkoxy or lower-alkyl radical; n is the integer 1, 2 or 3; Acyl is an acyl radical; and the term "lower" as used herein means the radical contains from 1 to 6 carbon atoms; and the acid addition and quaternary ammonium salts thereof; with the provisos that (i) when W is unsubstituted phenyl, and A is lower alkylene, and R^1 is lower alkyl, and R^3 is unsubstituted or substituted phenyl then the ring system

is a piperidine ring; and (ii) when W is a substituted or unsubstituted, 5 or 6-membered heteroaryl radical, and A is a $-CH_2CH_2-$ radical and R^1 is hydrogen or lower alkyl, then R^3 is other than lower alkyl; in conjunction with a non-toxic carrier; with the further proviso that when W is unsubstituted phenyl, and A is methylene or ethylene, and R^1 is hydrogen, and R^3 is phenyl, which may be substituted or unsubstituted, phenyl-lower-alkyl or lower alkyl, and

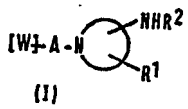


is a piperidine ring, then the carrier excludes water and common organic solvent as sole carrier.

It is to be understood that the term "alkylene" used herein includes both straight and branched chain radicals, the term "lower" means the radical concerned contains 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms and by the term "aryl or heteroaryl radical" is meant a radical possessing aromatic character.

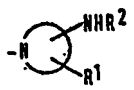
The compounds of formula I(a) contained in the above pharmaceutical compositions exhibit pharmacological activity for example anti-inflammatory activity and/or action on the cardiovascular system (such as hypotensive and/or anti-hypertensive activity) and/or anti-histamine activity and sometimes central nervous system activity (such as sedative or anti-convulsant activities) when tested on warm-blooded animals.

A second aspect of the invention is the provision of certain novel compounds of general formula

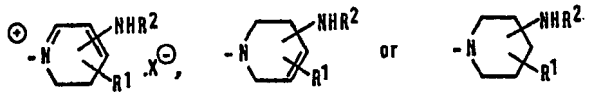


(I)

in which

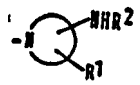


represents a ring system of the general formula



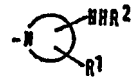
II(a) II(b) II(c)

W, A, R^1, Acyl, the term "lower", and n have the meanings as defined in connection with formula I(a); $X^{\ominus}$ is an anion; and R^2 is hydrogen or the group —COR, when



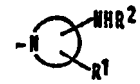
represents a ring system of formula II(a) or II(c) and the group —COR when

represents a ring system of formula II(b) wherein R represents a substituted or unsubstituted aryl radical (including heteroaryl radicals), aryloxy, aryl-lower-alkyl, aryl-lower-alkyloxy, diaryl-lower-alkyl, cyclo-alkyl containing five to seven ring carbon atoms, lower alkoxy, or lower alkyl; and the acid addition and quaternary ammonium salts of those compounds wherein

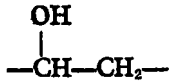


represents a ring system of formula II(b) or II(c); with the provisos that (i) when W is unsubstituted phenyl, and A is lower alkylene and R^1 is lower alkyl, and R^2 is —COR wherein R is unsubstituted or substituted phenyl then the ring system

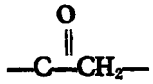
is a ring system of formula II(a) or II(c); (ii) when W is unsubstituted phenyl, and A is methylene or ethylene, and R^1 is hydrogen, and R^2 is hydrogen or the group —COR wherein R is phenyl, which may be substituted or unsubstituted, phenyl-lower-alkyl, or lower alkyl, then the ring system



is a ring system of formula II(a) or II(b); (iii) when W is a substituted or unsubstituted 5 or 6 membered heteroaryl radical, and A is a

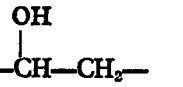


or $—CH_2CH_2—$ radical, and R^1 is hydrogen or lower alkyl, then R^2 is the group —COR wherein R is other than lower alkyl; (iv) when W is a phenyl or a 5 or 6 membered hetero-aryl radical both of which may be substituted or unsubstituted, and A is a



radical, and R^1 is hydrogen, and the ring system

is a ring system of formula II(a), then R^2 is the group —COR wherein R is other than lower alkyl; and (v) when W is substituted or unsubstituted phenyl and A is a



radical, and R^1 is hydrogen or lower alkyl, then R^2 is the group —COR wherein R is other than lower alkyl.

Certain of these compounds have useful pharmaceutical properties as mentioned above, i.e. when compounds of formula I have a structure within the definition of formula I(a). In addition, compounds of formula I in which R^2 is hydrogen and/or

is a ring system of formula II(a) are intermediates for the other compounds of formula I, which in turn can act as intermediates for other compounds of formula I.

Examples of W are unsubstituted phenyl or phenyl substituted by one or more groups, which may be the same or different selected from halogen (for example fluorine, chlorine or bromine), lower alkyl (for example methyl, ethyl, propyl, or butyl), lower alkoxy (for example methoxy, ethoxy, propoxy or butoxy), nitro, amino (including alkyl or dialkyl substituted amino groups) in particular dialkylamino (for example dimethylamino or diethylamino), acylamino in particular alkanoylamino [for example acetylamino (acetamido)], hydroxyl, carboxyl, lower alkoxycarbonyl, alkylenedioxy (for example methylenedioxy), trihaloalkyl (for example trifluoromethyl), mercapto, methylthio, methylsulphonyl, phenyl and phenyl substituted by one or more of those substituents mentioned immediately above in connection with the substituted phenyl group W. Further examples of W are cycloalkyl (for example cyclohexyl), 1,2,3,4-tetrahydronaphth-6-yl), naphthyl and indenyl radicals which may be unsubstituted or substituted as described above for the substituted phenyl group W, and heterocyclic radicals such as thienyl (for example 2-thienyl), benzo[b]thienyl (for example 3-benzo[b]thienyl), furyl, pyrrolyl (for example 3-pyrrolyl), imidazolyl (for example 4-imidazolyl), pyrazolyl (for example 4-pyrazolyl, pyridyl (for example 2- and 4-pyridyl), pyrimidinyl (for example 4-pyrimidinyl), quinolyl (for example 2-quinolyl), thiazolyl (for example 2-, 4- and 5-thiazolyl), isothiazolyl, oxazolyl, isoxazolyl, benzimidazolyl (for example 2-benzimidazolyl), benzo-1,4-dioxanyl (for example benzo-1,4-dioxan-2-yl) and benzindolyl in particular benz[g]indolyl (for example 3-benz[g]indolyl), which heterocyclic radicals may be unsubstituted or substituted as described above for the substituted phenyl group W. Examples of A are methylene, ethylene, propylene butylene, oxoethylene, oxalyl, oxo-propylene, hydroxyethylene and hydroxypropylene. Examples of R^1 are hydrogen, fluorine, chlorine, bromine, methyl, ethyl, propyl and butyl. Examples of R are the same as those already described for the aryl and heteroaryl radicals W and also methoxy, ethoxy, propoxy, butoxy, phenoxy, benzyl, phenethyl, benzyloxy, diphenylmethyl, cyclopentyl, cyclohexyl, cycloheptyl, methyl, ethyl, propyl and butyl. Examples of acid addition salts are those formed from inorganic and organic acids in particular pharmaceutically acceptable acid addition salts such as the sulphate, hydrochloride, hydrobromide, hydro-iodide, nitrate, phosphate, sulphonate (such as the methane-sulphonate and *p*-toluene-sulphonate), acetate, maleate, fumarate, tartrate and formate.

The compounds of general formula (I) can be prepared in a number of ways by building up the molecule from suitable starting materials in known manner. Such processes applied to the preparation of the novel compounds of formula (I) are included in the scope of the invention.

One method of preparation of compounds of general formula (I) in which R^2 is the —COR group and A is other than the oxime, aminoguanidone, or substituted

or unsubstituted hydrazone of a mono- or di-keto-lower alkylene radical, comprises reacting a compound of the general formula

III(a) III(b) III(c)

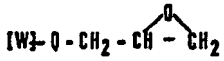
with an alkylating or acylating agent of the general formula

$$[W—]—A—Y \qquad (IV)$$

(where R, R^1, W and A have the meanings already defined and Y is a halogen atom or an equivalent replaceable atom or radical, for example an organic sulphonyl radical such as tosyl radical. As an alternative, the compounds of formula III(b) or III(c) may be reacted with (i) a compound of the formula

$$[W—]—A^1—H \qquad (V)$$

wherein the chain A^1 contains an epoxide residue for example



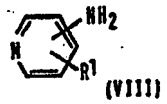
(VI)

to give a compound of formula (I) wherein the chain A is substituted by a hydroxyl radical, or (ii) an alkenyl compound of formula

$$[W]—B \qquad (VII)$$

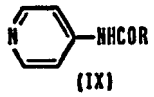
wherein B is a straight or branched chain alkenyl radical, preferably a vinyl radical to give a corresponding compound of formula (I) wherein A is a straight or branched chain alkylene radical.

The compounds of general formula (IV), (V), (VI) and (VII) are known compounds or can be made following the methods known for preparing compounds of these types. The starting materials of general formulae III(a), III(b) and III(c) can generally be made by acylating a corresponding amino compound of the general formula



(VIII)

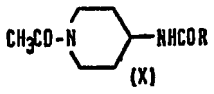
and if necessary reducing the ring system to the corresponding tetrahydropyridine or piperidine ring. The starting material of general formula III(c) in which —NHCOR is in the 4-position is preferably prepared by either (i) forming the oxime of an N-benzyl-4-piperidone, reducing to give the 4-amino compound, acylating the amino group and then hydrogenolysing the benzyl residue, or (ii) treating the pyridine of formula



(IX)

with a benzyl halide, for example benzyl chloride to give the quaternary salt, reducing with an alkali metal borohydride to give the corresponding N-benzyl-tetra-hydropyridine which is further subjected to concomitant de-benzylation and reduction of

the 3,4-double bond by catalytic hydrogenation, or (iii) catalytic hydrogenation of compound (IX) in the presence of acetic anhydride to give

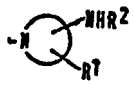


(X)

and then selectively hydrolysing the acetyl group.

A second general method of preparation of compounds of formula (I) in which

represents a ring system of formula II(a) or II(c) and R^2 is the —COR group, comprises reacting a corresponding compound of formula (I) in which R^2 is a hydrogen atom, with either a reactive derivative of an acid of general formula R . COOH (where R is aryl, heteroaryl, aryl-lower-alkyl, diaryl-lower-alkyl, cycloalkyl or lower alkyl), or with a halo-ester of formula Hal . CO . R (where Hal is a halogen atom and R is lower-alkoxy, aryloxy or aryl-lower-alkoxy). As a reactive derivative of the acid of formula R . COOH used in the process described above, we have found is preferable usually to use a halide (for example the chloride or bromide) or an anhydride. Other examples of reactive derivatives of the acid R . COOH which may be used are the acid azide, mixed anhydrides and active esters. Furthermore, the compounds of formula (I) in which



is a ring system of formula II(a) or II(c) and R^2 is the —COR group may also be prepared by treating a corresponding compound of formula (I) in which R^2 is a hydrogen atom with the acid R . COOH in the presence of a known condensing agent (for example, a carbodiimide), or by first activating the amino function (for example, by forming the phosphazo derivative) and then reacting with the acid R . COOH. In connection with the introduction of the —COR group into a compound of formula (I) in which R^2 is a hydrogen atom, reference may be made to "Chemistry of the Amino Acids" by Greenstein and Winitz (John Wiley & Sons, Inc., Publishers, 1961) at pages 782—883 and 943—1108.

When the compounds of general formula (I) are desired in which

represents a ring system of formula II(b) or II(c), R^2 is the —COR group and A is a lower alkylene or a mono- or di-keto lower alkylene radical or a bivalent radical of the formula

$$—N(\text{Acyl}) . CH_2 . C{\equiv}C . CH_2—,$$

the preparation may comprise a Mannich reaction using formaldehyde, a compound of formula III(b) or III(c) as secondary amine and either a compound WH (where W has the meanings already defined and thus WH can be considered as a compound formed by addition of a hydrogen atom to the radical W; said compound WH also containing a suitable reactive site of the type known in the literature to participate in the Mannich reaction), or a derivative of W in which the chain A has already been partially formed, and which partially formed chain contains a site of the type known

in the literature to participate in the Mannich reaction. Examples of the latter type of derivative are

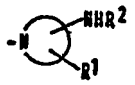
$$[W—]—CH_3, \quad [W—]—CO\,.\,CH_3$$

and

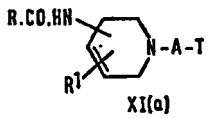
$$[W—]—N(\text{Acyl})—CH_2—C\equiv CH,$$

which derivatives are known compounds or can be made following the methods known for preparing compounds of these types. The formaldehyde used in the above reaction may be in the form of a solution in an inert solvent or as paraformaldehyde.

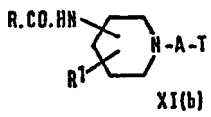
The tetrahydropyridine and piperidine compounds of general formula (I) in which



is a ring system of formula II(b) or II(c), R^2 is the —COR group and A is other than the oxime, aminoguanidone, or substituted or unsubstituted hydrazone of a mono- or di-keto lower alkylene radical, may be prepared by starting with a compound of formula



XI(a)

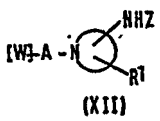


XI(b)

wherein T is a known precursor group of W and reacting with another molecule of the type known in the literature for the formation of W. Reference may be made in this connection to standard textbooks of Organic Chemistry such as: Organic Chemistry by Paul Karrer (Elsevier Publishing Company, Inc., 1950); Organic Chemistry by Fieser & Fieser (Reinhold Publishing Corporation, 1956); Chemistry of Carbon compounds by Rodd (Elsevier), Amsterdam, 1951—1969); Heterocyclic Compounds edited by Elderfield (John Wiley & Sons, Inc., 1950—1968); and Chemistry of the Heterocyclic Compounds edited by Weissberger (Interscience, 1954). As examples of T may be mentioned —COOAlkyl, —$CO\,.\,CH_2\,.\,OH$ and —$CH_2\,.\,CH(OAlkyl)_2$ where Alkyl represents a lower alkyl radical. As examples of reactants known to react with T may be mentioned, *o*-phenylenediamine, *l*-naphthylhydrazine or a mixture of formaldehyde and ammonia. The compounds of formula XI(a) and XI(b) may be made following methods known in the art for the preparation of similar compounds.

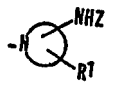
When it is desired to prepare a compound of general formula (I) wherein

is a ring system of formula II(a) or II(c), R^2 is a hydrogen atom and A is other than the oxime, aminoguanidone, or substituted or unsubstituted hydrazone or a mono- or di-keto lower alkylene radical, a corresponding compound of formula

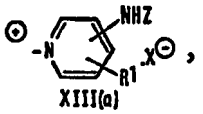


(XII)

(wherein W, and R^1 have the meanings defined in connection with formula (I),

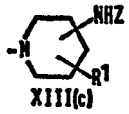


represents a ring system of formula



XIII(a)

or

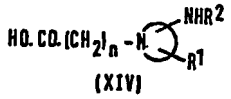


XIII(c)

and Z is a protecting group known in the art for the protection of the amino function and A has the meanings defined immediately above), is subjected to hydrolysis, hydrogenolysis or some other reaction known in the art for the removal of the protecting group Z. As examples of Z, mention is made of those wherein Z is the group —COR and R is lower alkyl, lower alkoxy and aryloxy (particularly methyl, ethoxy and phenoxy respectively). Other examples of Z are benzyl, *p*-toluene-sulphonyl, phthalyl, trityl, trifluoroacetyl, formyl and benzylsulphonyl. Reference may be made to the review of protecting groups in Advances in Organic Chemistry, *3*, 191—294 (Interscience Publishers 1963), and also to Chemistry of the Amino Acids by Greenstein and Winitz, Vol. 2, pages 885—924 (John Wiley & Sons, Inc., 1961). The compounds of general formula (XII) can be prepared following the information already given but using the appropriate acylating agent or other reagent to introduce the group Z.

A further aspect of the invention is the provision of a process for the preparation of compounds of formula (I) in which

is a ring system of formula II(b) or II(c) and A is the —NH . CO . $(CH_2)_n$— group wherein n is the integer 1, 2, or 3, in which process a reactive derivative (as herein before described) of an acid of formula

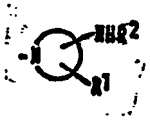


(XIV)

is reacted with a primary amine of formula

$$[W]—NH_2 \qquad (XV)$$

[in which, n is 1, 2 or 3,



has the formula II(b) or II(c) and W, R^1 and R^2 have the meanings defined in connection with formula (I)].

A still further aspect of the invention is the provision of a further process for the preparation of compounds of general formula (I) in which

represents a ring system of formula II(b) or II(c), W and R^1 have the meanings defined

in connection with formula (I), R^2 is the group —COR, R has the meanings defined in connection with formula (I) and A is a lower alkylene radical or the bivalent radical —NH . CO . $(CH_2)_n$— in which n is 1, 2 or 3, and wherein the process consists of reacting a compound of the general formula

[W]—A—OH (XVI)

(in which W, and A have the meanings defined immediately above) with a compound of formula III(b) or III(c) (in which R^1 and R^2 have the meanings defined immediately above).

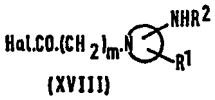
The reaction is preferably carried out in the presence of a catalyst, for example Raney Nickel. An organic solvent, which is inert under the reaction conditions, is usually used for example xylene, toluene or benzene. Preferably the reaction is carried out by heating the reactants under reflux in a water-immiscible organic solvent, for example xylene, and removing the water formed during the reaction by azeotropic distillation. If necessary, reactive substituent groups can be blocked during a reaction and released later.

In order to prepare a compound of formula (I) in which

represents a ring system of formula II(b) or II(c), W and R^1 have the meanings defined in connection with formula (I), R^2 is the —COR group wherein R has the meanings defined in connection with formula (I) and A is a mono-keto lower-alkylene radical of formula —CO . $(CH_2)_m$— in which m is 1 to 5, a compound of formula

[W]—H (XVII)

is acylated (Friedel-Crafts) with an acid halide of formula



(XVIII)

For details of the reaction, reference may be made to "The Friedel-Crafts and related reactions", by G. A. Olah, Vol. 3 (Interscience Publishers, 1964).

The reactions outlined above usually are carried out in a solvent which is inert under the reaction conditions. The most suitable solvent system is chosen and varies depending on the particular reactants being employed. If necessary heating the reactants in solution under reflux can be carried out, and if necessary heating under high pressures may also be used.

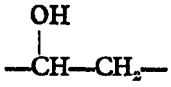
Once a compound of general formula (I) has been prepared, then if necessary one or more substituents in the molecule may be converted to another substituent each within its own meanings specified in connection with formula (I). If a compound is produced in which

represents the pyridinium ring system of formula II(a), this may be selectively reduced to one of the other ring systems of lower oxidation state. For example when R^2 is the —COR group, reduction with an alkali metal borohydride gives the tetrahydropyridine ring system of formula II(b). On the other hand when R^2 is H or the group —COR, catalytic hydrogenation, for example, in the presence of Raney nickel or a platinum

catalyst, gives rise to the piperidine ring system of formula II(c). Similarly if a compound of formula (I) is prepared in which

represents the tetrahydropyridine ring system of formula II(b), this may also be reduced to the piperidine ring system of formula II(c) wherein R^2 is the —COR.

If a compound of formula (I) is prepared in which the chain A contains one or more carbonyl functions, then this chain may be selectively reduced. For example, when A is the oxalyl residue —CO . CO—, this may be reduced under mild conditions such as by a hydride transfer agent (particularly lithium aluminium hydride) to give the



residue. When A is the —CO—CH_2— residue this may be reduced with an alkali metal borohydride to give the

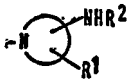
residue. When the oxalyl residue is reduced under more drastic conditions, the ethylene chain —CH_2—CH_2— results.

If a compound of formula (I) is produced in which

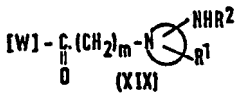
is a ring system of formula II(a) or II(c) and R^2 is the —COR group, if necessary this may be hydrolysed to the corresponding compound of formula (I) in which R^2 is a hydrogen atom and which may then be reacted to give a corresponding compound of formula (I) in which R^2 is a different —COR group.

When a compound of formula (I) is produced wherein the radical W has one or more methoxy substituents, hydrolysis to the corresponding hydroxyl compound may be brought about in known manner. Furthermore, if the radical W has a nitro substituent this may be reduced in known manner to the corresponding amino compound which in turn may be further acylated or alkylated.

In order to prepare a compound of general formula (I) in which W, R^1, R^2 and R have the meanings defined in connection with formula (I),



represents a ring system of formula II(a), II(b) or II(c) and A is the oxime, aminoguanidone or substituted or unsubstituted hydrazone of a mono-keto- lower alkylene radical, the corresponding ketone of general formula



(XIX)

(in which W, R^1, R^2, R and

have the meanings defined immediately above and m is 1 to 5) is converted into the desired derivative by methods known in the literature. In this respect reference may

be made to (1) Reagents for Organic Synthesis by L. Fieser and M. Fieser (John Wiley & Sons, Inc., 1967) at page 434 and 479; (2) U.K. Patent Specification 1,223,491; and (3) A Scheme of Qualitative Organic Analysis by F. J. Smith and E. Jones (Blackie & Son Ltd., 1960) at page 38.

If necessary, in any of the reactions hereinbefore described, reactive substituent groups may be blocked during a reaction and released at a later stage. As already indicated the novel tetrahydropyridine and piperidine compounds provided by the invention contain a basic nitrogen atom and thus can form acid addition salts with acids (particularly pharmaceutically acceptable acids) or quaternary ammonium salts, for example with alkyl halides or aralkyl halides (particularly methyl iodide or benzyl chloride or bromide). The acid addition salts may either be formed *in situ* during the hereinbefore described processes and isolated therefrom or a free base may be treated with the appropriate acid in the presence of a suitable solvent and then the salt isolated. The quaternary salts may be prepared by treating the free base with the appropriate halide in the presence or absence of a solvent.

As already mentioned, the pharmaceutical compositions of the invention contain as active ingredients a compound of formula I(a) as hereinbefore defined, which may be micronised. In addition to the active ingredient, said compositions also contain a non-toxic carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a solid and a liquid. Solid form compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, binders, or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 to 99, preferably 10—80% of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low melting wax, and cocoa butter. The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly cachets are included.

Sterile liquid form compositions include sterile solutions, suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilised by intramuscular, intraperitoneal or subcutaneous injection. In many instances a compound is orally active and can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage form can be a packaged composition, the package containing specific quantities of compositions, for example packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in package form. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from 5 mg. of less to 500 or more, according to the particular need and the activity of the active ingredient. The invention also includes the compounds in the absence of carrier where the compounds are in unit dosage form.

The following non-limiting Examples illustrate the invention:

EXAMPLE 1

1-[2-(Cyclohexy)ethyl]-4-benzamidopiperidine

2-Cyclohexylethyl bromide (1.9 g.) in dimethylformamide (10 ml. was added to 4-benzamidopiperidine (2.2 g.), di-isopropylamine (4 ml.) and a trace of sodium iodide

in dimethylformamide (10 ml.). The mixture was heated at 70°C for 16 hours, cooled, poured into water, and extracted with methylene chloride. The washed and dried extracts were evaporated and the solid residue was recrystallised from ethanol to give the product (1.25 g.), m.p. 174—5°C. (Found: C, 76.4; H, 9.5; N, 8.9. $C_{20}H_{30}N_2$ requires C, 76.4; H, 9.6; N, 8.9%).

EXAMPLE 2

1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-acetamidopyridinium iodide

1-(2-Iodoethyl)-3,4-dimethoxybenzene (29.3 g.) and 4-acetamidopyridine (14.0 g.) in absolute ethanol (100 ml.) were refluxed for 2.5 hours. The resulting crystalline material was collected and recrystallised from ethanol to give the title compound (29.1 g.), m.p. 201—202°C. (Found: C, 47.9; H, 4.9; N, 6.3; $C_{17}H_{21}IN_2O_3$ requires C, 47.7; H, 4.9; N, 6.5%).

EXAMPLE 3

1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-acetamidopiperidine

The quaternary salt of Example 2 (50 g.) and W7 Raney nickel (*ca.* 30 g.) in ethanol (600 ml.) containing triethylamine (13.1 g.) was hydrogenated at 700 p.s.i. and 80°C. for 4 hours. The filtrate, after removal of the catalyst was evaporated to dryness. Trituration of the residue with 2N sodium hydroxide solution caused crystallisation of 30.1 g. of the title compound, m.p. 152—4°C. (Found: C, 66.4; H, 8.6; N, 9.1. $C_{17}H_{24}N_2O_3$ requires C, 66.6; H, 8.6; N, 9.1%).

EXAMPLE 4

1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-aminopiperidine

The acetamido compound of Example 3 (2.5 g.) in 2N hydrochloride acid (25 ml.) was heated under reflux for 3.5 hours. The cooled solution was basified and extracted with chloroform. Evaporation of the washed and dried extracts gave an oil which was treated with ethanolic hydrogen chloride to provide 1.67 g. of the title compound as its dihydrochloride, m.p. 260—263°C. (Found: C, 53.4; H, 7.7; N, 8.3. $C_{15}H_{24}N_2O_2 . 2HCl$ requires C, 53.3; H, 7.8; N, 8.3%).

EXAMPLE 5

1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-benzamidopiperidine

The amine dihydrochloride of Example 4 (2.0 g.) in methylene chloride (100 ml.) was stirred with potassium carbonate (2.76 g.) in water (50 ml.). Benzoyl chloride (1.8 ml.) in methylene chloride (20 ml.) was added slowly dropwise. Stirring was continued for 2 hours. The aqueous layer was separated and extracted with methylene chloride. Evaporation of the washed and dried methylene chloride layers gave an oil which was crystallised from ethanol to provide 1.80 g. of the title compound, m.p. 194—195°C. (Found: C, 71.7; H, 7.7; N, 7.5. $C_{22}H_{28}N_2O_3$ requires C, 71.7; H, 7.7; N, 7.6%).

EXAMPLE 6

1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-(2-chlorobenzamido)-piperidine

The title compound as its hydrochloride (m.p. 250—2°C) was prepared in the same way as for the compound of Example 5 but using *o*-chlorobenzoyl chloride in place of benzoyl chloride. (Found: C, 60.2; H, 6.1; N, 6.3. $C_{22}H_{25}Cl N_2O_3 . HCl$ requires C, 60.3; H, 6.2; N, 6.4%).

EXAMPLE 7

1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-piperonyloylaminopiperidine

The title compound hydrochloride dihydrate (m.p. 285—8°C) was prepared in the same way as for the compound of Example 5 but utilising piperonyloyl chloride in place of benzoyl chloride. (Found: C, 57.1; H, 6.8; N, 5.7. $C_{23}H_{28}N_2O_5 . HCl . 2H_2O$ requires C, 57.0; H, 6.8; N, 5.8%).

EXAMPLE 8

1-[2-(3,4,5-Trimethoxyphenyl)ethyl]-4-benzamidopiperidine

Prepared in exactly the same way as for the compound of Example 1 except that 3,4,5-trimethoxyphenethyl chloride was used in place of cyclohexylethyl bromide. The title compound was obtained as a monohydrate (1.2 g.), m.p. 193—4°C. (Found: C, 66.7; H, 7.6; N, 6.9. $C_{20}H_{30}N_2O_4 . H_2O$ requires C, 66.4; H, 7.5; N, 6.7%).

EXAMPLE 9

1-[2-(3,4-Dihydroxyphenyl)ethyl]-4-benzamidopiperidine

4 - Benzamido - 1 - [2 - (3,4 - dimethoxyphenyl)ethyl]piperidine (12.2 g.) in dry

methylene chloride (400 ml.) was added dropwise with stirring to a solution of boron tribromide (40 g.) in dry methylene chloride (120 ml.) at −50°C. The reaction mixture was kept at room temperature for 48 hours, then water was added with stirring. The resulting precipitate was collected and crystallised from ethanol. Recrystallisation from ethanol-ether gave the title compound as the hydrobromide, hemihydrate (6.0 g.), m.p. 256—257°C. (Found: C, 56.1; H, 5.9; N, 6.4. $C_{20}H_{24}N_2O_3 . HBr . \frac{1}{2}H_2O$ requires C, 55.8; H, 6.1; N, 6.5%).

EXAMPLE 10

1-Phenacyl-4-benzamidopiperidine

Phenacyl bromide (2 g.), 4-benzamidopiperidine (2 g.) and potassium carbonate (2 g.) in isopropanol (25 ml.) were heated under reflux for 2 hours. The resulting solid was filtered, suspended in water and re-filtered to give the product (1.57 g.), m.p. 168°C. (Found: C, 74.4; H, 6.8; N, 8.8. $C_{20}H_{22}N_2O_2$ requires C, 74.5; H, 6.9; N, 8.7%).

EXAMPLE 11

1-[2-(3,4-Dihydroxyphenyl)-2-oxoethyl]-4-benzamidopiperidine

A mixture of 3,4-dihydroxyphenacyl chloride (18.65 g.), 4-benzamidopiperidine (20.40 g.) and potassium carbonate (20.7 g.) in isopropanol (400 ml.) was stirred under reflux for 2 hours, cooled, and filtered. The resulting solid was suspended in water, stirred for 30 minutes and filtered again to give the product as a quarter hydrate (11.24 g.), m.p. 219.5°C. (dec.) (Found: C, 66.8; H, 6.2; N, 7.5. $C_{20}H_{22}N_2O_4 . \frac{1}{4}H_2O$ requires C, 66.9; H, 6.3; N, 7.8%).

EXAMPLE 12

1-[2-(1-Naphthyl)ethyl]-4-benzamidopiperidine

1-(2-Bromoethyl)naphthalene (3.0 g.) was added to a solution of 4-benzamidopiperidine (3.0 g.), di-isopropylamine (4 ml.) and a trace of sodium iodide in dimethylformamide (10 ml.). The mixture was heated at 70°C overnight, then poured into water and extracted with methylene chloride. The washed and dried extracts were evaporated and the residue was recrystallised from benzene to give the title compound (3.0 g.), m.p. 160—162°C. (Found: C, 80.5; H, 7.4; N, 7.5. $C_{24}H_{26}N_2O$ requires C, 80.4; H, 7.3; N, 7.8%).

EXAMPLE 13

1-[2-(2-Naphthyl)ethyl]-4-benzamidopiperidine

Prepared in a similar manner to the compound of Example 12 but using 2-(2-bromoethyl)-naphthalene in place of the 1-isomer. The product (m.p. 190—3°C) was crystallised from isopropanol. (Found: C, 80.5; H, 7.5; N, 7.7. $C_{24}H_{26}N_2O$ requires C, 80.4; H, 7.3; N, 7.8%).

EXAMPLE 14

1-[2-(3-Indenyl)ethyl]-4-benzamidopiperidine

3-(2-Bromoethyl)indene (1.12 g.), 4-benzamidopiperidine (1.02 g.) and potassium carbonate (1.38 g.) were heated under reflux in isopropanol (25 ml.) for 24 hours. The mixture was filtered and the filtrate was evaporated. Trituration of the residue with ether gave a solid which was recrystallised twice from aqueous ethanol to provide the title compound, m.p. 148—149°C. (Found: C, 79.7; H, 7.6; N, 8.0. $C_{23}H_{26}N_2O$ requires C, 79.7; H, 7.6; N, 8.1%).

EXAMPLE 15

1-[3-(3-Indenyl)propyl]-4-benzamidopiperidine

Prepared in a similar manner to the compound of Example 14 but using 3-(3-bromopropyl)indene in place of 3-(2-bromoethyl)indene. The title compound crystallised from isopropanol, m.p. 157—9°C. (Found: C, 79.8; H, 8.1. N, 7.7. $C_{24}H_{28}N_2O$ requires C, 80.0; H, 7.8; N, 7.8%).

EXAMPLE 16

1-[2-(4-Pyridyl)ethyl]-4-benzamidopiperidine

A mixture of 4-vinylpyridine (578 mg.), 4-benzamidopiperidine (1.02 g.), acetic acid (330 mg.) and methanol (5 ml.) was refluxed for 8 hours, cooled, and evaporated. The residue in water was basified with potassium carbonate and the resulting solid was collected. Recrystallisation from aqueous ethanol gave the product (1.24 g.) m.p. 193—5°C. (Found: C, 73.3; H, 7.4; N, 13.3. $C_{19}H_{23}N_3O$ requires C, 73.75; H, 7.4; N, 13.3%).

EXAMPLE 17

1-[2-(4-Pyrimidinyl)ethyl]-4-benzamidopiperidine

4-Benzamidopiperidine hydrochloride (2.4 g.), water (1.0 ml.), 4-methylpyrimidine (0.94 g.) and 39.4% aqueous formaldehyde (0.80 ml.) were mixed in the order listed and heated on a steam bath for 1 hour then left overnight at room temperature. The reaction mixture was brought to pH8 with 2N sodium hydroxide solution and extracted with chloroform. Evaporation of the dried extracts gave a solid which was dissolved in ethanol and made just acid with ethanolic hydrogen chloride. Crystallisation occurred on cooling and recrystallisation from ethanol provided the product hydrochloride, m.p. 221—222°C. (Found: C, 62.3; H, 6.8; N, 15.9. $C_{18}H_{22}N_4O$. HCl requires C, 62.35; H, 6.7; N, 16.1%).

EXAMPLE 18

1-[2-(4-Imidazoylyl)ethyl]-4-benzamidopiperidine

(a) 4-Benzamidopiperidine (2.4 g.) in ethanol (15 ml.) was added to hydroxymethyl-vinyl ketone (2.0 g.). An exothermic reaction occurred and crystallisation occurred on cooling to give 2-(4-benzamidopiperidino)ethyl hydroxymethyl ketone, m.p. 154—155°C. (Found: C, 65.9; H, 7.7; N, 9.5. $C_{16}H_{22}N_2O_3$ requires C, 66.2; H, 7.6; N, 9.65%).

(b) The foregoing product (3.0 g.) in ethanol (10 ml.) was added to a mixture of cupric acetate (5 g.), 0.880 ammonia (40 ml.) and 40% aqueous formaldehyde (3 ml.). The reaction mixture was heated on a steam bath for 1 hour. The copper salt was collected, suspended in hot water and brought to pH3. Hydrogen sulphide was passed in until there was no further precipitation then the mixture was filtered and the filtrate was evaporated. Trituration of the residue with ethanol gave the product as a dihydrochloride, hydrate, m.p. 228—230°C. (Found: C, 52.45; H, 6.7; N, 14.4. $C_{17}H_{22}N_4O$. 2HCl . H_2O requires C, 52.4; H, 6.7; N, 14.4%).

EXAMPLE 19

1-(2-Pyrrolyl-oxalyl)-4-benzamidopiperidine

A solution of redistilled pyrrole (13.4 g.) in ether (50 ml.) was added to a stirred solution of oxalyl chloride (20 ml.) in ether (250 ml.) at −50°C. Stirring and cooling were maintained for 1 hour, then the solution was poured into a vigorously stirred mixture of sodium bicarbonate (100 g.) in water (600 ml.) and 4-benzamidopiperidine (80 g.) in chloroform (400 ml.). The reaction mixture was kept at 0°C for 40 hours, then the solid was filtered off and recrystallised from ethanol-water to give the product hydrate (80 g.), m.p. 124—5°C. (Found: C, 63.0; H, 6.2; N, 12.2. $C_{18}H_{19}N_3O_3$. H_2O requires C, 63.0; H, 6.2; N, 12.2%).

EXAMPLE 20

1-[2-Hydroxy-2-(2-pyrrolyl)ethyl]-4-benzamidopiperidine

The product of Example 19 (3.4 g.) in tetrahydrofuran (80 ml.) was added to a stirred suspension of lithium aluminium hydride (1.9 g.) in tetrahydrofuran (100 ml.). When the addition was complete the suspension was heated under reflux for 3 hours. Water (5.5 ml.) was added dropwise and the inorganic material was filtered off. Evaporation of the filtrate and recrystallisation of the residue from ethanol gave the product (2.5 g.) m.p. 138—139°C. (Found: C, 69.1; H, 7.7; N, 13.2. $C_{18}H_{23}N_3O_2$ requires C, 69.0; H, 7.4; N, 13.4%).

EXAMPLE 21

1-[3-(1-Phenyl-5-methylpyrazol-4-yl)-3-oxopropyl]-4-benzamidopiperidine

4-Acetyl-5-methyl-1-phenylpyrazole (4.0 g.), 4-benzamidopiperidine (4.08 g.), concentrated hydrochloric acid (3.0 ml.) and paraformaldehyde (1.8 g.) were dissolved in ethanol (50 ml.) and heated under reflux for 24 hours. The solution was concentrated and water was added to induce crystallisation. Recrystallisation of the crude product (4.27 g.) from isopropanol gave the hydrochloride, hydrate, m.p. 181—3°C. (Found: C, 63.8; H, 6.6; N, 12.05. $C_{25}H_{28}N_4O_2$. HCl . H_2O requires C, 63.75; H, 6.6; N, 11.9%).

EXAMPLE 22

1-[2-(3-Benzo[b]thienyl)ethyl]-4-benzamidopiperidine

(a) 3-(2-Hydroxyethyl)benzo[b]thiophene (2.8 g.) in anhydrous pyridine (31 ml.) at −15°C. was stired while *p*-toluenesulphonyl chloride (3.29 g.) was added portionwise. One hour later, water was added, keeping the temperature below −10°C. The aqueous

layer was decanted off and the residual oil was dissolved in methanol and kept at 0°C. overnight, whereupon 3-(2-tosyloxyethyl)benzo[b]thiophene (1.71 g., m.p. 56—8°C) crystallised. (Found: C, 61.3; H, 4.8. $C_{17}H_{16}O_3S_2$ requires C, 61.4; H, 4.85%).

(b) A mixture of the foregoing tosylate (1.25 g.), 4-benzamidopiperidine (0.77 g.) and potassium carbonate (1.04 g.) in isopropanol (19 ml.) was heated under reflux for 17 hours. The hot reaction mixture was filtered and the filtrate was allowed to cool. The resulting crystals were recrystallised from ethanol made just acid with ethanolic hydrogen chloride to give the product hydrochloride, hemihydrate, m.p. 242—245°C. (Found: C, 64.4; H, 6.2; N, 7.1. $C_{22}H_{24}N_2OS \cdot HCl \cdot \frac{1}{2}H_2O$ requires C, 64.45; H, 6.4; N, 6.8%).

EXAMPLE 23

1-[2-(2-Quinolyl)ethyl]-4-benzamidopiperidine

2-(2-Hydroxyethyl)quinoline (5.0 g.) in thionyl chloride (15 ml.) was heated at 50°C. for 30 minutes. Excess thionyl chloride was removed and the residue was added to 4-benzamidopiperidine (4.74 g.) and potassium carbonate (12.0 g.) in dimethylformamide (25 ml.). The reaction mixture was stirred under reflux for 18 hours, cooled and shaken with water and ether. The ether extracts were dried and evaporated and the residue in acetonitrile was acidified with dry hydrogen chloride to give the product as the dihydrochloride, m.p. 198°C. (dec). (Found: C, 63.7; H, 6.3; N, 9.7. $C_{23}H_{25}N_3O \cdot 2HCl$ requires C, 63.9; H, 6.3; N, 9.7%).

EXAMPLE 24

1-[N-(5-Ethoxycarbonyl-4-phenylthiazol-2-yl)carbamoylmethyl]-4-benzamidopiperidine

A mixture of 2 - (3 - chloroacetamido) - 5 - ethoxycarbonyl - 4 - phenylthiazole 3.25 g.), 4-benzamidopiperidine (2.04 g.) and triethylamine (1.11 g.) in dimethylformamide (50 ml.) was stirred at room temperature for 18 hours. Water and ice were added and the solid was filtered off. Recrystallisation from ethanol gave the product (2.95 g.), m.p. 189—190°C. (Found: C, 63.5; H, 5.7; N, 11.25. $C_{26}H_{28}N_4O_4S$ requires C, 63.4; H, 5.7; N, 11.4%).

EXAMPLE 25

1-[N-(2-Methylphenyl)carbamoylethyl]-4-benzamidopiperidine

A mixture of 3-chloropropion-*o*-toluidine (2.0 g.), 4-benzamidopiperidine (2.0 g.) and potassium carbonate (2.76 g.) in isopropanol (50 ml.) was stirred and heated under reflux for 18 hours. The hot mixture was filtered and the filtrate allowed to cool. The product (1.85 g., m.p. 195—7°C) crystallised out. (Found: C, 72.6; H, 7.5; N, 11.5. $C_{22}H_{27}N_3O_2$ requires C, 72.3; H, 7.45; N, 11.5%).

EXAMPLE 26

1-[4-(N-Propionyl-N-[2,6-dichlorophenyl]amino)but-2-yn-1-yl]-4-benzamidopiperidine

(a) 2,6-Dichloroaniline (27.75 g.) in pyridine (100 ml.) was stirred and ice cooled while propionyl chloride (17.5 g.) was added dropwise. Stirring was continued for 1 hour then the solid was filtered off and the filtrate was evaporated. Trituration with ether/water gave a white solid (27.35 g.) which was recrystallised from aqueous ethanol to give 2,6-dichloropropionanilide (21.35 g.), m.p. 155—7°C. Found: C, 49.8; H, 4.25; Cl, 32.5. $C_9H_9Cl_2NO$ requires C, 49.8; H, 4.1; Cl, 32.4%).

(b) The foregoing amide (3.59 g.) suspended in dry ether (25 ml.) was added with stirring to sodamide prepared from sodium (420 mg.) in liquid ammonia (*ca.* 40 ml.). Stirring was continued for 1 hour then propargyl bromide (2.16 g.) in ether (5 ml.) was added slowly. The ammonia was allowed to evaporate and water was added. The aqueous layer was twice reextracted with ether and the combined ether layers were dried and evaporated. Recrystallisation of the residue from light petroleum (b.p. 60—80°C) gave N-propargyl-2,6-dichloropropionanilide (3.02 g.), m.p. 78—9°C. (Found: C, 56.1; H, 4.4; Cl, 27.6. $C_{12}H_{11}Cl_2NO$ requires C, 56.3; H, 4.3; Cl, 27.7%).

(c) A mixture of the foregoing acetylene (2.56 g.), 4-benzamidopiperidine (2.04 g.), paraformaldehyde (330 mg.) and cuprous chloride (20 mg.) in dioxane (10 ml.) was heated on a steam bath for 3.5 hours, cooled and evaporated. Recrystallisation of the residue from benzene-light petroleum gave the product (2.36 g.), m.p. 136°C. (Found: C, 63.7; H, 5.7; N, 8.9. $C_{25}H_{27}Cl_2N_3O_2$ requires C, 63.6; H, 5.8; N, 8.9%).

EXAMPLE 27

1-[1-(4-Acetamidophenoxy)-2-hydroxyprop-3-yl]-4-benzamidopiperidine

A solution of 2,3-epoxy-1-(4-acetamidophenoxy)-propane (5.18 g.) and 4-benzamidopiperidine (6.13 g.) in isopropanol (250 ml.) was refluxed for 24 hours, cooled

and a white crystalline solid was filtered off (8.90 g.). This was recrystallised from isopropanol to give 7.41 g. of the title compound as a quarter hydrate, m.p. 226—8°C. (Found: C, 66.35; H, 7.1; N, 10.1. $C_{23}H_{29}N_3O_4 . \frac{1}{4} H_2O$ requires C, 66.4; H, 7.15; N, 10.1%).

EXAMPLE 28

1-(5-Acetamido-2-hydroxybenzyl)-4-benzamidopiperidine

4-Acetamidophenol (1.51 g.) and 39.4% aqueous formaldehyde (1.25 ml.) were dissolved in 50% aqueous ethanol, and 4-benzamidopiperidine (2.04 g.) was added. The resulting solution was heated under reflux for 30 minutes then left overnight at room temperature. The white solid was collected and purified by suspending in boiling ethanol and filtering to give the title compound (1.32 g.), m.p. 242°C. (Found: C, 68.15; H, 7.1; N, 11.3. $C_{21}H_{25}N_3O_3$ requires C, 68.6; H, 6.9; N, 11.4%).

EXAMPLE 29

1-[4-(4-Fluorophenyl)-4-oxobutyl]-4-benzamidopiperidine

4-Benzamidopiperidine (2.0 g.), 4′-chloro-*p*-fluorobutyrophenone (1.0 g.) and a trace of sodium iodide in dimethylformamide (5 ml.) were maintained at 70°C for 18 hours. On cooling, the solid which separated was collected, suspended in water, and refiltered. Recrystallisation from ethanol-water gave the title compound (0.52 g.), m.p. 161—2°C. (Found: C, 71.9; H, 6.85; N, 7.5. $C_{22}H_{25}FN_2O_2$ requires C, 71.7; H, 6.8; N, 7.6%).

EXAMPLE 30

1-[2-(3-Benz[g]indolyl)ethyl]-4-benzamidopiperidine

(a) 4-Benzamidopiperidine (62 g.) was added to a stirred suspension of 1.1 g. cupric acetate and 9.5 g. paraformaldehyde in 300 ml. dry dioxane, followed by propiolaldehyde diethylacetal (38.6 g.). Stirring was continued for 24 hours at 80°C under nitrogen. The hot reaction mixture was filtered and the filtrate was evaporated. Recrystallisation of the solid residue from ethyl acetate-petroleum ether (bp. 60—80°C) gave 4-benzamido-1-(4,4-diethoxybut-2-ynyl)piperidine as colourless shining leaflets (84.6 g.), m.p. 130°C. (Found: C, 69.5; H, 8.3; N, 8.3. $C_{20}H_{28}N_2O_3$ requires C, 69.7; H, 8.2; N, 8.1%).

(b) The foregoing product (70 g.) in absolute ethanol (1 l.) was hydrogenated in the presence of 10% palladium-on-carbon (7 g.) at 50 p.s.i. hydrogen pressure for 30 minutes. Evaporation of the filtrate after removing the catalyst, and recrystallisation of the residue from petroleum ether (b.p. 60—80°C) gave 1-(4,4-diethoxybutyl)-4-benzamidopiperidine as colourless leaflets (61.29 g.), m.p. 95°C. (Found: C, 69.0; H, 9.2; N, 8.2. $C_{20}H_{32}N_2O_3$ requires C, 68.9; H, 9.3; N, 8.0%).

(c) 1-(4,4-Diethoxybutyl)-4-benzamidopiperidine (3.48 g.) was added portionwise to a solution of 1-naphthylhydrazine hydrochloride (1.95 g.) in 25% aqueous acetic acid (15 ml.) with stirring at 80°C. Stirring and heating were continued for 2.5 hours, then the mixture was left for 3 days at room temperature to precipitate the crude product (1.28 g.). Recrystallisation from ethanol gave the title compound as the hydrochloride, hemihydrate, m.p. 285°C (dec). (Found: C, 70.2; H, 6.75; N, 9.2; $C_{26}H_{27}N_3O . HCl . \frac{1}{2}H_2O$ requires C, 70.5; H, 6.6; N, 9.3%).

EXAMPLE 31

1-[2-(2-Pyridyl)ethyl]-4-benzamidopiperidine

A mixture of 2-vinylpyridine (5.78 g.), 4-benzamidopiperidine (10.20 g.) and acetic acid (3.30 g.) in methanol (50 ml.) was heated under reflux for 8 hours. The methanol was removed under reduced pressure, the residue was dissolved in water, cooled, and basified with potassium carbonate to precipitate the free base. The solid in ethanol was made just acid with ethanolic hydrogen chloride to give the title compound as the dihydrochloride, quater hydrate (13.12 g.), m.p. 202—3°C. (Found: C, 58.95; H, 6.6; N, 10.9. $C_{19}H_{23}N_3O . 2HCl . \frac{1}{4} H_2O$ requires C, 59.0; H, 6.9; N, 10.9%).

EXAMPLE 32

1-(2-Hydroxy-2-phenylethyl)-4-benzamidopiperidine

Sodium borohydride (6.00 g.) in 0.2N NaOH solution (60 ml.) was added dropwise to a stirred solution of 1 - (2 - phenyl - 2 - oxoethyl) - 4 - benzamidopiperidine (4.83 g.) in methanol (300 ml.). After refluxing the solution for 2 hours it was filtered and the filtrate concentrated to *ca.* 100 ml., whereupon the product crystallised out to give the title compound, m.p. 178—180°C. (Found: C, 74.1; H, 7.5; N, 8.6. $C_{20}H_{24}N_2O_2$ requires C, 74.0; H, 7.5; N, 8.6%).

EXAMPLE 33

1-[2-(5-Phenylthien-2-yl)ethyl]-4-benzamidopiperidine

(a) Butyl lithium was prepared from lithium (8.6 g.) in ether (300 ml.) and butyl bromide 68.5 g.) at −10°C. Unreacted lithium was filtered off and an ethereal solution of 2-phenylthiophene (32.25 g.) was added. The mixture was refluxed for 1 hour then cooled to 5°C. Ethylene oxide (15 g.) in ether (30 ml.) was added dropwise and the mixture was refluxed for 2 hours, then left overnight at room temperature. Water was added, followed by dilute hydrochloric acid and the aqueous layer was extracted with fresh ether. Evaporation of the combined, washed and dried ether layers gave a solid residue which was recrystallised from benzene-light petroleum to give 2-(2-hydroxyethyl)-5-phenylthiophene (31.6 g.), m.p. 71—2°C.

(b) The foregoing product (6.12 g.) in pyridine (50 ml.) was stirred at −20°C while *p*-toluene-sulphonyl chloride (6.30 g.) was added. Stirring was continued overnight at room temperature then the solution was cooled to −10°C. and water (130 ml.) was slowly added. The resulting solid was recrystallised from methanol to give 2-(2-tosyloxyethyl)-5-phenylthiophene (3.78 g.), m.p. 93°C.

(c) The foregoing product (3.59 g.) was added to a mixture of 4-benzamidopiperidine (2.04 g.) and potassium carbonate (2.07 g.) in isopropanol (50 ml.) and the resulting mixture was stirred and heated under reflux overnight. The hot suspension was filtered, and the filtrate allowed to stand at 0°C. for 2 hours, whereupon the product (1.23 g.) crystallised. Recrystallisation from ethanol gave the title compound, m.p. 161—2°C. (Found: C, 73.9; H, 6.75; N, 7.1. $C_{24}H_{26}N_2OS$ requires C, 73.8; H, 6.7; N. 7.2%).

EXAMPLE 34

1-[2-(2-Benzimidazolyl)ethyl]-4-benzamidopiperidine

(a) A mixture of 4-benzamidopiperidine (2.00 g.), ethyl 3-bromopropionate (1.30 ml.) and potassium carbonate (2.00 g.), in isopropanol (25 ml.) was refluxed for 18 hours, filtered while hot, and the filtrate allowed to cool. The crystalline product was collected to give 1-(2-ethoxycarbonylethyl)-4-benzamidopiperidine (1.93 g.), m.p. 112—3°C.

(b) The foregoing product (3.16 g.) was added to o-phenylenediamine (1.08 g.) in 4N hydrochloric acid (10 ml.) and the solution was refluxed for 2 hours, cooled, and filtered. Basification of the filtrate gave the crude product as a precipitate which was recrystallised from ethanol to give the title compound as a quarter hydrate, m.p. 241—3°C (dec). (Found: C, 71.3; H, 7.3; N, 15.5. $C_{21}H_{24}N_4O \cdot \frac{1}{4} H_2O$ requires C, 71.5; H, 7.0; N, 15.9%).

EXAMPLE 35

1-[3-(1-Naphthoxy)-2-hydroxyprop-1-yl]-4-benzamidopiperidine

3-(α-Naphthoxy)-1-chloropropan-2-ol (1.18 g.) was refluxed for 16 hours in isopropyl alcohol (100 ml.) with 4-benzamidopiperidine (1.032 g.) and anhydrous potassium carbonate (1.037 g.). The mixture was filtered hot, cooled and evaporated to dryness. The gum so obtained gave the title compound as a solid on triturating in ether, m.p. 139—141°C. (Found: C, 74.1; H, 7.1; N, 6.9. $C_{25}H_{28}N_2O_3$ requires C, 74.2; H, 7.0; N, 6.9%).

EXAMPLE 36

1-[2-(p-Nitrophenyl)ethyl]-4-benzamidopiperidine

p-Nitrophenylethyl bromide (1.15 g.) was refluxed for 20 hours in isopropyl alcohol (75 ml.) with 4-benzamidopiperidine (1.032 g.) and anhydrous potassium carbonate (1.037 g.). The mixture was filtered hot, refrigerated and product was filtered off (547 mg.), washed with cold isopropyl alcohol and ether. The filtrate was evaporated to yield more product (1.4 g.). Recrystallisation from a mixture of benzene and petroleum ether (b.p. 40—60°C) gave the title compound, m.p. 209—216°C.

(Found: C, 68.2; H, 6.7; N, 11.8. $C_{20}H_{23}N_3O_3$ requires C, 68.0; H, 6.6; N, 11.9%).

EXAMPLE 37

1-[2-(p-Aminophenyl)ethyl]-4-benzamidopiperidine

1-[2-(*p*-Nitrophenyl)ethyl]-4-benzamidopiperidine (3.0 g.) was hydrogenated in absolute alcohol (400 ml) at 50 p.s.i. and 20°C for 3 hours in the presence of 300 mg. of platinum oxide as catalyst. The catalyst was filtered off and the solution evaporated to give the crude product as a foam. Crystallisation from a mixture of benzene and n-hexane gave the title compound, m.p. 193—195°C. (Found: C, 74.4; H, 7.9; N, 12.9. $C_{20}H_{25}N_3O$ requires C, 74.3; H, 7.8; N, 13.0%).

EXAMPLE 38

1-[2-(*p*-Acetamidophenyl)ethyl]-4-benzamidopiperidine

1-[2-(*p*-Aminophenyl)ethyl]-4-benzamidopiperidine (2.3 g.) was refluxed for 2 hours with acetic anhydride (22 ml.) in anhydrous pyridine (100 ml.). The solution was refrigerated for 24 hours and a crystalline product was filtered off, which after washing with ether yielded the title compound, m.p. 270—275°C (dec). (Found: C, 72.6; N, 7.55; N, 11.6. $C_{22}H_{27}N_3O_2$ requires C, 72.3; H, 7.45; N, 11.5%).

EXAMPLE 39

1-[2-Phenethyl]-4-benzamidopyridinium bromide

A solution of 4-benzamidopyridine (7.92 g.) and 2-phenethyl bromide (9.25 g.) in absolute ethanol (100 ml.) was refluxed for 7.5 hours. Ether (100 ml.) was added and the mixture was allowed to stand overnight. The title compound (8.33 g.), m.p. 200—203°C, was filtered off. (Found: C, 62.7; H, 5.0; N, 7.3. $C_{20}H_{19}BrN_2O$ requires C, 62.7; H, 5.0; N, 7.35%).

EXAMPLE 40

1-Phenethyl-4-benzamido-1,2,5,6-tetrahydropyridine

4-Benzamido-1-phenethylpyridinium bromide (3.0 g.) in methanol (100 ml.) was treated with sodium borohydride (6.0 g.) in portions over 30 minutes. The solution was stirred during the addition and for 1 hour after. Water was then added to the warmed solution until crystallisation commenced to give the title compound (2.15 g.), m.p. 115—7°C. (Found: C, 78.2; H, 7.3; N, 9.1. $C_{20}H_{22}N_2O$ requires C, 78.4; H, 7.2; N, 9.1%).

EXAMPLE 41

1-[2-(4-[*p*-Chlorophenyl]-2-phenylthiazol-5-yl)ethyl]-4-benzamidopiperidine.

A mixture of 5 - (2 - chloroethyl) - 4 - (*p* - chlorophenyl) - 2 - phenylthiazole (10.0 g.), 4-benzamidopiperidine (6 g.), anhydrous potassium carbonate (8.4 g.) suspended in isopropylalcohol (100 ml.) was heated under reflux for 17 hours. The mixture was filtered and the filtrate evaporated to give an oil which crystallised from aqueous ethanol to give yellow needles of the title compound (3.0 g.), m.p. 199—200°C. (Found: C, 69.2; H, 5.7; N, 8.2: $C_{29}H_{28}ClN_3OS$ requires C, 69.4; H, 5.6; N, 8.4%).

EXAMPLE 42

1-[2-(*p*-Chlorophenyl)thiazol-4-yl]methyl-4-benzamidopiperidine.

A mixture of 2-(*p*-chlorophenyl)-4-chloromethylthiazole (1.83 g.), 4-benzamidopiperidine (1.53 g.) and triethylamine (0.85 g.) in dimethylformamide (25 ml.) was stirred at room temperature for 18 hours, and then poured into water (400 ml.). The precipitated white solid was collected by filtration, washed thoroughly with water followed by ether, and dried *in vacuo* at 60°C., to give 2.65 g. of the title compound, m.p. 219—220°C. (Found: C, 64.2; H, 5.4; N, 10.0. $C_{22}H_{22}ClN_3OS$ requires C, 64.1; H, 5.4; N, 10.2%).

EXAMPLE 43

The following compounds were prepared in a similar manner to that described in the hereinbefore disclosed Examples and processes:—

1-(2-Phenylprop-1-yl)-4-benzamidopiperidine.
1-(2-Phenylbut-1-yl)-4-benzamidopiperidine.
1-(3-Phenylprop-2-yl)-4-benzamidopiperidine.
1-(4-Phenylbut-3-yl)-4-benzamidopiperidine.
1-(3-Phenylbut-2-yl)-4-benzamidopiperidine.
1-[4-(Quinol-2-yl)but-1-yl]-4-benzamidopiperidine.
1-[5-(Quinol-2-yl)pent-1-yl]-4-benzamidopiperidine.
1-[6-(Quinol-2-yl)hex-1-yl]-4-benzamidopiperidine.
1-[(Quinol-2-yl)eth-1-yl]-4-benzamidopiperidine.
1-[(Quinol-2-yl)prop-1-yl]-4-benzamidopiperidine.
1-[(Quinol-2-yl)but-1-yl]-4-benzamidopiperidine.
1-(3-Cyclohexylbut-1-yl)-4-benzamidopiperidine.
1-[2-Cyclohexylmethylprop-1-yl]-4-benzamidopiperidine.
1-[4-Cyclohexylbut-2-yl]-4-benzamidopiperidine.
1-[2-(*o*-Chlorophenyl)ethyl]-4-benzamidopiperidine.
1-[2-(*o*- and *p*-Methylphenyl)ethyl]-4-benzamidopiperidine.
1-[2-(*o*- and *p*-Ethylphenyl)ethyl]-4-benzamidopiperidine.

1-[2-(*o*- and *p*-Propylphenyl)ethyl]-4-benzamidopiperidine.
1-[2-(*o*- and *p*-Butylphenyl)ethyl]-4-benzamidopiperidine.
1-[2-(*p*-Dimethylaminophenyl)ethyl]-4-benzamidopiperidine.
1-[2-(*p*-Diethylaminophenyl)ethyl]-4-benzamidopiperidine.
1-[2-(*p*-Ethoxycarbonylphenyl)ethyl]-4-benzamidopiperidine.
1-[2-(*p*-Carboxyphenyl)ethyl]-4-benzamidopiperidine.
1-Benzyl-4-acetamidopiperidine.
1-(2,6-Dichlorophenylmethyl)-4-benzamidopiperidine.
1-(2,6-Dichlorophenylethyl)-4-benzamidopiperidine.
1-[2-(2-Naphthyloxy)ethyl]-4-benzamidopiperidine.
1-[3-(2-Naphthyloxy)propyl]-4-benzamidopiperidine.
1-[2-(*m*-Trifluoromethylphenyl)ethyl]-4-benzamidopiperidine.
1-[2-(*p*-Diphenyl)ethyl]-4-benzamidopiperidine.
1-[2-(3,4-Methylenedioxyphenyl)ethyl]-4-benzamidopiperidine.
1-(2-Cyclopentylethyl)-4-benzamidopiperidine.
1-(2-Cycloheptylethyl)-4-benzamidopiperidine.
1-[2-(7-Carbethoxymethoxy-4-methyl-2-oxo-chromen-3-yl)ethyl]-4-benzamidopiperidine.

EXAMPLE 44

1-Phenethyl-4-benzamidopiperidine

(a) A solution of 4-benzamidopyridine (7.92 g.) and 2-phenethyl bromide (9.25 g.) in absolute ethanol (100 ml.) was refluxed for 7.5 hours. Ether (100 ml.) was added and the mixture was allowed to stand overnight. 4-Benzamido-1-phenethylpyridinium bromide (8.33 g.), m.p. 200—203°C was filtered off. (Found: C, 62.7; H, 5.0; N, 7.3. $C_{20}H_{19}BrN_2O$ requires C, 62.7; H, 5.0; N, 7.35%).

(b) The quaternary salt (2.0 g.) in 95% ethanol (300 ml.) containing triethylamine (2.0 ml.) was hydrogenated in the presence of W7 Raney nickel catalyst (*ca.* 2 g.) at 400 p.s.i. and 85°C for 7 hours. The catalyst was filtered off and the filtrate was evaporated. Trituration of the residue with 2N sodium hydroxide solution gave a cream solid which was recrystallised from aqueous ethanol to provide the title compound (1.06 g.), m.p. 164—166°C. (Found: C, 77.8; H, 8.0; N, 9.2. Calculated for $C_{20}H_{24}N_2O$ C, 77.9; H, 7.8; N, 9.1%).

Dissolution of the free base in ethanol and treatment with ethanolic hydrogen chloride followed by ether gave the hydrochloride of the title compound. Other salts are prepared from the free base in a similar manner.

EXAMPLE 45

1 Phenethyl-4-acetamidopiperidine.

(a) A solution of phenethyl bromide and 4-acetamidopyridine in absolute ethanol was heated under reflux, cooled, treated with ether and allowed to stand overnight to give 1-phenethyl-4-acetamidopyridinium bromide.

(b) The above quaternary salt in ethanol containing triethylamine and W7 Raney nickel was hydrogenated at 400 p.s.i. and 80°C. The catalyst was then filtered off and the filtrate evaporated to dryness to give a residue which on triturating with 2N sodium hydroxide solution gave the title compound.

Dissolution of the free base in ethanol followed by treatment with ethanolic hydrogen chloride and ether gave the hydrochloride of the title compound.

EXAMPLE 46

1-Phenethyl-4-phenylacetamidopiperidine.

(a) The acetamido compound of Example 45 in 2N hydrochloric acid was heated under reflux for 3.5 hours, cooled, basified and extracted with chloroform. Evaporation of the washed and dried extracts gave a residue which on treating with ethanolic hydrogen chloride gave the corresponding acid addition salt of 1-phenethyl-4-aminopiperidine.

(b) The above amino compound was treated with phenacetyl chloride in a mixture of methylene chloride and water containing potassium carbonate to give the title compound. Acid addition salts were prepared in a similar manner to that described in Example 44.

EXAMPLE 47

1-Benzyl-4-benzamidopiperidine.

1-Benzyl-4-piperidone was converted into the corresponding oxime derivative which on reduction gave 1-benzyl-4-aminopiperidine. Treatment of the amino com-

pound with benzoyl chloride in a mixture of methylene chloride and water containing potassium carbonate afforded the title compound from which salts can be prepared in a similar manner to that described in Example 44.

EXAMPLE 48

1-Benzyl-4-(*p*-chlorobenzamido)piperidine.

The 1-benzyl-4-aminopiperidine prepared in Example 47 was treated with *p*-chlorobenzoyl chloride in a similar manner to that described in the same example and the product converted to a salt.

EXAMPLE 49

1-Benzyl-4-(*p*-methylbenzamido)piperidine.

The 1-benzyl-4-aminopiperidine prepared in Example 47 was treated with *p*-methylbenzoyl chloride in a similar manner to that described in the same example and the product converted to a salt.

EXAMPLE 50

1-[2-(*o*-Nitrophenyl)ethyl]-4-benzamido-piperidine.

A mixture of 2-(*o*-nitrophenyl)ethyl bromide (1.15 g.), 4-benzamidopiperidine (1.02 g.) and potassium carbonate (1.04 g.) in isopropanol (75 ml.) was stirred and refluxed for 24 hours. The hot mixture was filtered, the filtrate evaporated and the residue crystallised from ethanolic hydrogen chloride and ether to give the title compound as the hydrochloride, (47 mg.), m.p. 236—241°C. (Found: C, 61.31; H, 6.1; N, 10.6. $C_{20}H_{23}N_3O_3$. HCl requires C, 61.6; H, 6.2; N, 10.8%).

EXAMPLE 51

1-[(3,4-Dichlorobenzoyl)methyl]-4-benzamidopiperidine.

A mixture of 3,4-dichlorophenyl chloromethyl ketone (2.24 g.), 4-benzamidopiperidine (2.04 g.) and triethylamine (1.11 g.) was stirred in dry dimethylformamide (60 ml.) at room temperature for 18 hours. The solution was evaporated and the residue was crystallised from ethanolic hydrogen chloride and ether to give the title compound as the hydrochloride (1.45 g.), m.p. 226°C. (Found: C, 56.3; H, 5.3; N, 6.8. $C_{20}H_{20}Cl_2N_2O_2$. HCl requires H, 56.15; H, 4.95; N, 6.55%).

EXAMPLE 52

1-[2-(*o*-Aminophenyl)ethyl]-4-benzamidopiperidine.

A solution of 1-[2-(*o*-nitrophenyl)ethyl]-4-benzamidopiperidine (4.25 g.) in absolute ethanol (150 ml.) was added over 50 minutes to stirred stannous chloride (10.82 g.) in concentrated hydrochloric acid (12 ml.) and water (7.5 ml.) at 60—70°C. After addition, the mixture was stirred at this temperature for 4 hours before cooling and evaporating the ethanol. Continuous extraction into chloroform of the neutralised (with 2N sodium hydroxide solution) aqueous fraction gave the title compound (1.65 g.). The aqueous layer after extraction was made alkaline with 2N sodium hydroxide solution and extracted with more chloroform to give a further batch of the title compound (2.36 g.). The total product was crystallised from ethanolic hydrogen chloride and ether to give the hydrochloride of the title compound (2.75 g.), m.p. 263.8°C. (Found: C, 60.3; H, 7.0; N, 10.5. $C_{20}H_{25}N_3O$. 2HCl requires C, 60.6; H, 6.9; N, 10.60%).

EXAMPLE 53

1-[2-(3,4-Dichlorophenyl)-2-hydroxyethyl]-4-benzamido-piperidine.

Sodium borohydride (15.0 g.) in 0.2N sodium hydroxide solution (200 ml.) was added over 30 minutes to a stirred solution of 1-[(3,4-dichlorobenzoyl)methyl]-4-benzamidopiperidine monohydrochloride (6.45 g.) in methanol (260 ml.). Stirring was continued for 3 days after the addition, and the mixture was then refluxed for 2 hours. The precipitated product was filtered from the hot mixture, washed with cold water and dried to give 4.83 g. of the title compound. This was crystallised from ethanolic hydrogen chloride and ether to give the hydrochloride (4.86 g.) m.p. 270.0°C. (Found: C, 55.8; H, 5.5; N, 6.4. $C_{20}H_{22}Cl_2N_2O_2$. HCl requires C, 55.9; H, 5.4; N, 6.54%).

EXAMPLE 54

4-Benzamido-1-[2-(3,4-dichlorophenyl)-2-hydrazonoethyl]-piperidine.

1 - [(3,4 - Dichlorobenzoyl)methyl] - 4 - benzamidopiperidine monohydrochloride (19.2 g.) was dissolved in refluxing ethanol (1.2 l.). Hydrazine hydrate (100%, 8.97 g.) in water (40 ml.) was added and refluxing was continued for 10 hours. The reaction

mixture was cooled and the title compound (14.72 g.) was filtered off, m.p. 186—7°C. (Found: C, 59.3; H, 5.5; N, 13.9. $C_{20}H_{22}Cl_2N_4O$ requires C, 59.3; H, 5.5; N, 13.8%).

EXAMPLE 55

1-[2-(3,4-Dichlorophenyl)ethyl]-4-benzamidopiperidine.

4-Benzamidopiperidine (204 mg.) and anhydrous potassium carbonate (138 mg.) were intimately ground together and added to 2-(3,4-dichlorophenyl)ethyl bromide (254 mg.). The resulting paste was heated at 100°C for 2 hours to give a hard solid. This was broken up, washed well with water and ether and dried to give the title compound (355 mg.). Recrystallisation from ethanolic hydrogen chloride and ether gave the hydrochloride (237 mg.), m.p. 286.0°C. (Found: C, 58.2; H, 5.8; N, 6.8. $C_{20}H_{22}Cl_2N_2O$. HCl requires C, 58.05; H, 5.6; N, 6.8%).

EXAMPLE 56

1-[2-(2,6-Dichlorophenyl)ethyl]-4-benzamidopiperidine.

2-(2,6-Dichlorophenyl)ethyl bromide (674 mg.) was reacted with 4-benzamidopiperidine (547 mg.) in the presence of anhydrous potassium carbonate (736 mg.) following the procedure of Example 55 to give the title compound as the hydrochloride (412 mg.) m.p. 285.7°C after crystallisation from ethanolic hydrogen chloride and ether. (Found: C, 58.0; H, 5.6; N, 6.7. $C_{20}H_{22}Cl_2N_2O$. HCl requires C, 58.05; H, 5.6; N, 6.8%).

EXAMPLE 57

1-[3-Phenylpropyl]-4-benzamidopiperidine.

3-Phenylpropyl bromide (2.7 g.) was reacted with 4-benzamido-piperidine (3.39 g.) in the presence of anhydrous potassium carbonate (2.28 g.) following the procedure of Example 55 to give the title compound as the hydrochloride, quarter hydrate (1.96 g.), m.p. 237.2°C after crystallisation from ethanolic hydrogen chloride and ether. (Found: C, 69.6; H, 7.6; N, 7.6. $C_{21}H_{26}N_2O$. HCl . 1/4 H_2O requires C, 69.4; H, 7.6; N, 7.7%).

EXAMPLE 58

1-[4-(*p*-Fluorophenyl)-n-butyl]-4-benzamidopiperidine.

Hydrazine hydrate (80%, 60 ml.) was added to 1 - [4 - (*p* - fluorophenyl) - 4 - oxobutyl] - 4 - benzamidopiperidine (11.08 g.) dissolved in warm ethylene glycol (125 ml.) and the solution was refluxed gently for 60 minutes (135—140°C). Potassium hydroxide pellets were added (6.0 g.) and excess water and hydrazine were distilled off until the temperature rose to 185°C. Refluxing was continued for 30 minutes at this temperature and the hot solution was poured into cold water (500 ml.). The precipitated product was filtered off and after two crystallisations from ethanolic hydrogen chloride and ether the hydrochloride, hemihydrate of the title compound was obtained (1.85 g.) m.p. 228.3°C. (Found: C, 66.1; H, 7.4; N, 7.4. $C_{22}H_{27}FN_2O$. HCl . $\frac{1}{2}$ H_2O requires C, 66.1; H, 7.3; N, 7.0%).

EXAMPLE 59

1-[2-(3,4-Dimethylphenyl)ethyl]-4-benzamidopiperidine.

2-(3,4-Dimethylphenyl)ethyl bromide (4.57 g.) was combined with 4-benzamidopiperidine (4.09 g.) in the presence of anhydrous potassium carbonate (2.76 g.) following the procedure of Example 55 to give the hydrochloride, hydrate of the title compound (3.07 g.), m.p. 276.0°C. (Found: C, 67.9; H, 7.7; N, 7.1. $C_{22}H_{28}N_2O$. HCl . H_2O requires C, 67.6; H, 8.0; N, 7.2%).

EXAMPLE 60

4-Benzamido-1-[4-(p-fluorophenyl)-4-oxobutyl]-piperidine.

4-Chloro-4'-fluorobutyrophenone (5.5 g.) was reacted with 4-benzamidopiperidine (5.1 g.) in the presence of anhydrous potassium carbonate (3.45 g.) following the procedure of Example 55 to give the title compound as the hydrochloride (4.84 g.), m.p. 257.9°C from ethanolic hydrogen chloride and ether. (Found: C, 65.1; H, 6.5; N, 6.7. $C_{22}H_{25}FN_2O_2$. HCl requires C, 65.25; H, 6.2; N, 6.9%).

EXAMPLE 61

4-Benzamido-1-(4-phenyl-4-oxobutyl)piperidine.

γ-Chlorobutyrophenone (3.64 g.) was reacted with 4-benzamidopiperidine (4.08 g.) in the presence of anhydrous potassium carbonate (2.76 g.) following the procedure of Example 55 to give the title compound as the hydrochloride quarter hydrate (3.89

g.), m.p. 241.1°C from ethanolic hydrogen chloride and ether. (Found: C, 67.9; H, 7.1; N, 7.1. $C_{22}H_{26}N_2O_2 . HCl . 1/4\ H_2O$ requires C, 67.5; H, 7.1; N, 7.2%).

EXAMPLE 62

4-Benzamido-1-[4-(2,5-dimethylphenyl)-4-oxobutyl]piperidine.

4-Chloro-2,5-dimethylbutyrophenone (1.05 g.) was reacted with 4-benzamido-piperidine (1.02 g.) in the presence of anhydrous potassium carbonate (0.69 g.) following the procedure of Example 55 to give the title compound as the hydrochloride (0.80 g.), m.p. 190.0°C from ethanolic hydrogen chloride and ether. (Found: C, 69.45; H, 7.7; N, 6.55. $C_{24}H_{30}N_2O_2 . HCl$ requires C, 69.5; H, 7.5; N, 6.75%).

EXAMPLE 63

4-Benzamido-1-[4-(2,4-dimethylphenyl)-4-oxo-butyl]piperidine.

4-Chloro-2,4-dimethylphenylbutyrophenone (4.20 g.) was reacted with 4-benzamidopiperidine (4.08 g.) in the presence of anhydrous potassium carbonate (2.76 g.) following the procedure of Example 55 to give the title compound as the hydrochloride (2.92 g.), m.p. 215.2°C from ethanolic hydrogen chloride and ether. (Found: C, 69.1; H, 7.6; N, 6.5. $C_{24}H_{30}N_2O_2 . HCl$ requires C, 69.5; H, 7.5; N, 6.75%).

EXAMPLE 64

1-(4-Phenylbutyl)-4-benzamidopiperidine.

1-Bromo-4-phenylbutane (6.39 g.) and 4-benzamido-piperidine (6.12 g.) were reacted in the presence of anhydrous potassium carbonate (4.14 g.) following the procedure of Example 55 to give the title compound as the hydrochloride quater hydrate (8.10 g.), m.p. 240.7°C from ethanolic hydrogen chloride and ether. (Found: C, 69.8; H, 7.9; N, 7.2. $C_{22}H_{28}N_2O . HCl . 1/4\ H_2O$ requires C, 70.0; H, 7.9; N, 7.4%).

EXAMPLE 65

4-Benzamido-1-(3,4-methylenedioxybenzyl)piperidine.

3,4-Methylenedioxybenzyl chloride (5.76 g.), 4-benzamido-piperidine (6.89 g.) and anhydrous potassium carbonate (7.00 g.) were stirred at room temperature for 5 hours in isopropanol (50 ml.). Additional isopropanol (100 ml.) was added and stirring continued for 3 hours. The mixture was then heated to the boiling point and filtered whilst hot. Filtration provided the title compound as the hemi-hydrate (7.94 g.), m.p. 179.5—180.5°C. A second crop (1.23 g.) was obtained on concentration of the mother liquors. (Found: C, 69.2; H, 6.55; N, 8.2. $C_{20}H_{22}N_2O_3 . \frac{1}{2}\ H_2O$ requires C, 69.15; H, 6.7; N, 8.1%).

EXAMPLE 66

4-Benzamido-1-[2-(*p*-chlorophenyl)ethyl]piperidine.

2-(*p*-Chlorophenyl)ethanol *p*-toluenesulphonate ester (9.8 g.), 4-benzamido-piperidine (6.49 g.) and anhydrous potassium carbonate (8.78 g.) were refluxed in isopropanol (150 ml.) for 12 hours and the mixture filtered hot. On cooling, the filtrate deposited the title compound as colourless crystals, (5.4 g.), m.p. 190—195°C. (Found: C, 70.3; H, 6.9; N, 8.1. $C_{20}H_{23}ClN_2O$ requires C, 70.1; H, 6.8; N, 8.2%).

EXAMPLE 67

4-Benzamido-1-[2-(*p*-methoxyphenyl)ethyl]piperidine.

2-(*p*-Methoxyphenyl)ethanol *p*-toluenesulphonate ester (1.53 g.), 4-benzamido-piperidine (1.02 g.) and anhydrous potassium carbonate (1.10 g.) were refluxed in isopropanol (50 ml.) for 8 hours and the mixture worked up as in Example 66 to provide the title compound, which was further recrystallised from ethyl acetate as colourless needles (0.78 g.), m.p. 178°C. (Found: C, 74.7; H, 7.9; N, 8.45. $C_{21}H_{26}N_2O_2$ requires C, 74.5; H, 7.7; N, 8.3%).

EXAMPLE 68

N-Phenyl-4-(p-benzamidopiperid-1-yl)butyramide.

4-Benzamido-1-(3-methoxycarbonyl)propylpiperidine (5 g.) was refluxed in redistilled aniline (25 ml.) under nitrogen for 18 hours. Filtration of the cooled mixture afforded the title compound which provided a colourless crystalline hydrochloride hemihydrate from ethanolic hydrogen chloride and ether, (4.5 g.), m.p. 203°C. (Found: C, 64.4; H, 6.95; N, 10.2. $C_{22}H_{27}N_3O_2 . HCl . \frac{1}{2}\ H_2O$ requires C, 64.3; H, 7.1; N, 10.2%).

EXAMPLE 69

2-(4'-Benzamidopiperid-1-yl)methylbenzo-1,4-dioxan.

2-(Bromomethyl)benzo-1,4-dioxan (4.58 g.) and 4-benzamidopiperidine (4.08 g.)

were reacted in the presence of anhydrous potassium carbonate (2.76 g.) following the procedure of Example 55 to give the title compound as the hydrochloride (6.00 g.), m.p. 214.8°C. from ethanolic hydrogen chloride and ether. (Found: C, 64.7; H, 6.7; N, 7.15. $C_{21}H_{24}N_2O_3$. HCl requires C, 64.85; H, 6.5; N, 7.2%).

EXAMPLE 70

4-Benzamido-1-[4-(p-chlorophenyl)-4-oxobutyl]piperidine.

4-Chloro-4¹-chlorobutyrophenone (2.17 g.) was added to a well-ground mixture of 4-benzamidopiperidine (2.04 g.) and anhydrous potassium carbonate (1.38 g.) and the mixture heated at 100°C for 1 hour. The solid residue was slurried with hot water (100 ml.) for 3 hours, filtered, washed with ether and dried to give a cream coloured solid. This solid was dissolved in ethanolic hydrogen chloride, treated with ether and then cooled to 0°C to give the title compound as its hydrochloride (1.9 g.), m.p. 242—243°C. (Found: C, 62.8; H, 6.2; N, 6.55. $C_{22}H_{23}ClN_2O_2$. HCl requires C, 62.7; H, 6.0; N, 6.65%).

EXAMPLE 71

1-(2-Phenoxyethyl)-4-benzamidopiperidine.

2-Phenoxyethylbromide (2.01 g.), 4-benzamidopiperidine (2.04 g.) and anhydrous potassium carbonate (1.38 g.) were reacted together according to the procedure of Example 70. The title compound as its hydrochloride (2.06 g.) had m.p. 207°C. (Found: C, 67.0; H, 7.1; N, 7.7. $C_{20}H_{24}N_2O_2$. HCl requires C, 67.3; H, 7.1; N, 7.85%).

EXAMPLE 72

4-Benzamido-1-(4-phenyl-4-hydroxybutyl)piperidine.

4-Benzamido-(4-phenyl-4-oxobutyl)piperidine (3.4 g.) was dissolved in methanol (125 ml.) and a solution of sodium borohydride (6.0 g.) in 0.2 N sodium hydroxide (30 ml.) was added at room temperature over a period of 0.5 hours. The resulting mixture was stirred for a further 2 hours and then heated under reflux for 4 hours. The resulting mixture was filtered, the filtrate evaporated almost to dryness and then treated with water (100 ml.). The colourless solid was filtered off, washed with water, dried, dissolved in a small amount of ethanolic hydrogen chloride and treated with ether until crystallisation commenced. Filtration and drying gave 1.875 g. of the hydrochloride of the title compound, m.p. 221°C. (Found: C, 68.1; H, 7.4; N, 7.3. $C_{22}H_{28}N_2O_2$. HCl requires C, 67.9; H, 7.5; N, 7.2%).

EXAMPLE 73

1-[4-(*p*-Fluorophenyl)-4-hydroxybutyl]-4-benzamidopiperidine.

4 - Benzamido - 1 - [4 - (*p* - fluorophenyl) - 4 - oxobutyl]piperidine (7.4 g.) in methanol (100 ml.) was treated during 25 minutes at room temperature with a solution of sodium borohydride (20 g.) in 0.2 N sodium hydroxide (200 ml.). The resulting mixture was then worked up as in Example 72 to give the title compound as its hydrochloride, m.p. 241°C (decomp.). (Found: C, 65.35; H, 7.0; N, 6.9. $C_{22}H_{27}FN_2O_2$. HCl requires C, 64.9; H, 6.9; N, 6.9%).

EXAMPLE 74

1-[3-(1-Naphthyloxy)-propyl]-4-benzamidopiperidine.

The title compound as its hydrochloride, m.p. 228°C (decomp.), was prepared by the method of Example 71 using 3-naphthyloxypropyl bromide (2.07 g.), 4-benzamidopiperidine (1.8 g.) and anhydrous potassium carbonate (1.24 g.). (Found: C, 70.4; H, 7.0; N, 6.6. $C_{25}H_{28}N_2O_2$. HCl requires C, 70.65; H, 6.9; N, 6.6%).

EXAMPLE 75

1-[2-(1,2,3,4-Tetrahydro-6-naphthyl)-2-oxoethyl]-4-benzamidopiperidine.

A solution of 6-chloroacetyl-1,2,3,4-tetrahydronaphthalene (20.87 g.), 4-benzamidopiperidine (20.4 g.) and triethylamine (11.1 g.) in dimethylformamide (200 ml.) was stirred for 3 days at room temperature. The crystals which had formed during this time were then filtered off, washed and dried. A portion of this crystalline solid (4.0 g.) was dissolved in ethanol (50 ml.) and acidified with ethanolic hydrogen chloride to give 4.0 g. of the hydrochloride of the title compound, m.p. 270°C (decomp). (Found: C, 69.5; H, 7.2; N, 6.8; $C_{24}H_{28}N_2O_2$. HCl requires C, 69.8; H, 7.1; N, 6.8%).

EXAMPLE 76

1-[2-(1,2,3,4-Tetrahydro-6-naphthyl)-2-hydroxyethyl]-4-benzamidopiperidine.

The title compound as its hydrochloride, m.p. 253°C (decomp.), was prepared by

reduction of the free base of the compound obtained in Example 75 using sodium borohydride. The procedure is that described in Example 72. (Found: C, 69.7; H, 7.5; N, 6.6. $C_{24}H_{30}N_2O_2$. HCl requires C, 69.5; H, 7.5; N, 6.75%).

EXAMPLE 77

1-[4-(1,2,3,4-Tetrahydro-6-naphthyl)-4-oxobutyl]-4-benzamidopiperidine.

6-Chlorobutyryl-1,2,3,4-tetrahydronaphthalene (6.4 g.), 4-benzamidopiperidine (2.0 g.) and anhydrous potassium carbonate (1.38 g.) were reacted and worked up as described in Example 70 to give the hydrochloride of the title compound, m.p. 221°C. (Found: C, 68.4; H, 7.7; N, 6.0. $C_{26}H_{32}N_2O_2$. HCl . H_2O requires C, 68.0; H, 7.7; N, 6.1%.

EXAMPLE 78

1-Phenethyl-4-benzamidopiperidine hydrochloride.

The free base of Example 44 (7.4 g.) was dissolved in boiling ethanol (100 ml.), the solution filtered and the filtrate made acid by addition of ethanolic hydrogen chloride. On cooling, 7.0 g. of the quarter hydrate of the title compound were obtained, m.p. 281°C (decomp). (Found: C, 68.55; H, 7.5; N, 7.9. $C_{20}H_{24}N_2O$. HCl . 1/4 H_2O requires C, 68.6; H, 7.6; N, 8.0%).

EXAMPLE 79

4-Benzamido-1-phenethylpiperidine.

2-Phenylethanol (0.61 g., 0.005 mole), 4-benzamido-piperidine (1.02 g., 0.005 mole) and Raney Nickel (W7, *ca.* 2 g.) were stirred in xylene (50 ml.) and the mixture boiled under reflux for 16 hours. Liberated water was removed by means of a Dean and Stark apparatus. Filtration of the hot mixture provided a yellow solution which was stored at room temperature until crystallisation was complete. The title compound was obtained as cream needles (0.85 g.), m.p. 164—7°C.

EXAMPLE 80

4-Benzamido-1-[2-(2-naphthyl)ethyl]piperidine.

2-(2-Naphthyl)ethanol (3.44 g., 0.02 mole), 4-benzamidopiperidine (4.08 g., 0.02 mole) and Raney Nickel (W7 *ca.* 5 g.) were suspended in xylene (200 ml.) and the stirred mixture boiled under reflux for 16 hours. Liberated water was removed by means of a Dean and Stark apparatus. The mixture was filtered hot and evaporated to *ca* 100 ml. The resulting yellow solution was stored until crystallisation was complete. The title compound was obtained as off-white needles (3.30 g.), m.p. 189—191°C.

EXAMPLE 81

1-[2-(2-Naphthyl)ethyl]-4-benzamido-piperidine, dihydrochloride	10 mg.
Lactose	77.5 mg.
Dried Maize Starch	11.75 mg.
Magnesium Stearate	0.75 mg.

Tablets of the above composition were made by milling the active ingredient to 40 mesh (British Standard), sieving through a 40 mesh (British Standard) sieve, mixing the milled material with the other components, compressing to form tablets, re-granulating, sieving to 20 mesh (British Standard) and then recompressing to form tablets.

EXAMPLE 82

1-[2-(2-Naphthyl)ethyl]-4-benzamido-piperidine, dihydrochloride	2.5 mg.
Lactose	157.34 mg.
Dried Maize Starch	9 mg.
Alpine Talc	9 mg.
Aerofil (Registered Trade Mark)	1.8 mg.
Sodium Lauryl Sulphate	0.36 mg.

Capsules of the above were made up by thoroughly mixing together batches of the above ingredients, sieving to 40 mesh (British Standard) and filling hard gelatine capsules (180 mg.) with the mixture.

EXAMPLE 83

1-[2-(2-Naphthyl)ethyl]-4-benzamido-piperidine dihydrochloride	4 mg.
Dextrose	50 mg.
Water for injection	to 1 ml.

Solutions suitable for injection were made up from the above ingredients and then filtered.

EXAMPLE 84

4-Benzamido-1-(4-phenyl-4-oxobutyl)-piperidine, hydrochloride, quater-hydrate	10 mg.
Lactose	77.5 mg.
Dried Maize Starch	11.75 mg.
Magnesium Stearate	0.75 mg.

Tablets of the above composition were made by milling the active ingredient to 40 mesh (British Standard), sieving through a 40 mesh (British Standard) sieve, mixing the milled material with the other components, compressing to form tablets, re-granulating, sieving to 20 mesh (British Standard) and then re-compressing to form tablets.

EXAMPLE 85

4-Benzamido-1-[4-(4-chlorophenyl)-4-oxobutyl]piperidine hydrochloride	10 mg.
Lactose	77.5 mg.
Dried Maize Starch	11.75 mg.
Magnesium Stearate	0.75 mg.

Tablets of the above composition were made by milling the active ingredient to 40 mesh (British Standard), sieving through a 40 mesh (British Standard) sieve, mixing the milled material with the other components, compressing to form tablets, re-granulating, sieving to 20 mesh (British Standard) and then re-compressing to form tablets.

EXAMPLE 86

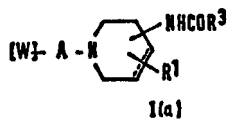
4-Benzamido-1-phenethylpiperidine	10 mg.
Lactose	77.5 mg.
Dried Maize Starch	11.75 mg.
Magnesium Stearate	0.75 mg.

Tablets of the above composition were made by milling the active ingredient to 40 mesh (British Standard), sieving through a 40 mesh (British Standard) sieve, mixing the milled material with the other components, compressing to form tablets, re-granulating, sieving to 20 mesh (British Standard), and then re-compressing to form tablets.

It is to be understood that any other of the compounds of the invention in the form of the free base or a pharmaceutically acceptable salt or quaternary ammonium salt thereof, may be used in place of the active ingredient of Examples 81 to 86.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising a heterocyclic compound of the general formula



1(a)

in which the dotted line represents an optional double bond; W represents a cycloalkyl radical containing five to seven ring carbon atoms or an aryl or heteroaryl radical other than an indolyl radical, all of which radicals may be substituted or unsubstituted; A represents a lower alkylene radical, a mono- or di-keto lower-alkylene radical or an

oxime, aminoguanidone or substituted or unsubstituted hydrazone derivative thereof, a hydroxy-lower-alkylene radical, or a bivalent radical of the formula

$$—NH—CO—(CH_2)_n—,$$

$$—N(\text{Acyl})—CH_2 . C{\equiv}C . CH_2—,$$

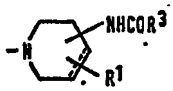
$$—O—CH_2CH(OH) . CH_2—$$

or

$$—O—(\text{lower-alkylene})—,$$

R^1 represents hydrogen, halogen or lower alkyl; R^3 represents a substituted or unsubstituted aryl radical (including heteroaryl radicals), aryl-lower-alkyl, diaryl-lower alkyl, cycloalkyl containing from five to seven ring carbon atoms, lower alkoxy or lower alkyl radical; n is the integer 1, 2 or 3; Acyl is an acyl radical; and the term "lower" means the radical contains from 1 to 6 carbon atoms; and the acid addition and quaternary ammonium salts thereof; with the provisos that (i) when W is unsubstituted phenyl, and A is lower alkylene, and R^1 is lower alkyl, and R^3 is unsubstituted or substituted phenyl then the ring system

is a piperidine ring; (ii) when W is a substituted or unsubstituted, 5 or 6 membered heteroaryl radical, and A is a $—CH_2CH_2—$ radical and R^1 is hydrogen or lower alkyl, then R^3 is other than lower alkyl; in conjunction with a non-toxic carrier; with the further proviso that when W is unsubstituted phenyl, and A is methylene or ethylene, and R^1 is hydrogen, and R^3 is phenyl, which may be substituted or unsubstituted, phenyl-lower-alkyl or lower-alkyl, and



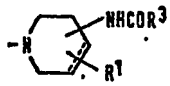
is a piperidine ring, then the carrier excludes water and common organic solvents as sole carrier.

2. A pharmaceutical composition according to Claim 1, wherein W is phenyl, A is an ethylene radical, R^3 is phenyl or benzyl and R^1 is hydrogen.

3. A pharmaceutical composition according to Claim 1, wherein W is phenyl, A is methylene, R^3 is phenyl, *p*-chlorophenyl or *p*-methylphenyl and R^1 is hydrogen.

4. A pharmaceutical composition according to Claim 1, wherein W is phenyl, A is an ethylene radical, R^3 is methyl and R^1 is hydrogen.

5. A pharmaceutical composition according to any one of Claims 2, 3 and 4, wherein



represents a piperidine ring, and R^1 and R^3 are as defined in any one of Claims 2, 3 or 4.

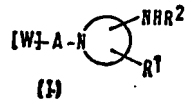
6. A pharmaceutical composition according to any one of Claims 1, 2 and 5, wherein the heterocyclic compound is 1-phenethyl-4-benzamidopiperidine.

7. A pharmaceutical composition according to any one of Claims 1 and 2, wherein the heterocyclic compound is 1-phenethyl-4-benzamido-1,2,5,6-tetrahydropyridine.

8. A pharmaceutical composition according to Claim 1, wherein the composition is in the form of a tablet or capsule.

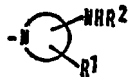
9. A pharmaceutical composition according to any one of Claims 2 to 7, wherein the composition is in the form of a tablet or capsule.

10. Heterocyclic compounds of the general formula

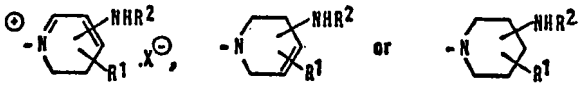


(I)

in which



represents a ring system of the general formula



II(a) II(b) II(c)

W represents a cycloalkyl radical containing five to seven ring carbon atoms or an aryl or heteroaryl radical other than an indolyl radical, all of which radicals may be substituted or unsubstituted; A represents a lower alkylene radical, a mono- or di-keto lower-alkylene radical or an oxime, aminoguanidone or substituted or unsubstituted hydrazone derivative thereof, a hydroxy-lower-alkylene radical, or a bivalent radical of the formula

$$-NH-CO-(CH_2)_n-,$$

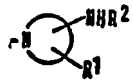
$$-N(Acyl)-CH_2 . C\equiv C . CH_2-,$$

$$-O-CH_2 . CH(OH) . CH_2-$$

or

$$-O-(\text{lower-alkylene})-;$$

R^1 represents hydrogen, halogen or lower alkyl; n is the integer 1, 2 or 3; Acyl is an acyl radical; $X^{\ominus}$ is an anion; R^2 is hydrogen or the group —COR when

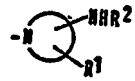


represents a ring system of formula II(a) or II(c) and the group —COR when

represents a ring system of formula II(b) wherein R represents a substituted or unsuostituted aryl radical (including heteroaryl radicals), aryloxy, aryl-lower-alkyl, aryl-lower-alkyloxy, diaryl-lower-alkyl, cycloalkyl containing five to seven ring carbon atoms, lower alkoxy or lower alkyl; and the term "lower" means that the radical con-

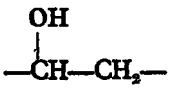
tains from 1 to 6 carbon atoms; and the acid addition and quaternary ammonium salts of those compounds wherein

represents a ring system of formula II(b) or II(c); with the provisos that (i) when W is unsubstituted phenyl, and A is lower alkylene, and R^1 is lower alkyl, and R^2 is —COR wherein R is unsubstituted or substituted phenyl then the ring system

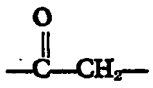


is a ring system of formula II(a) or II(c) and (ii) when W is unsubstituted phenyl, and A is methylene or ethylene, and R^1 is hydrogen, and R^2 is hydrogen or the group —COR wherein R is phenyl, which may be substituted or unsubstituted, phenyl-lower-alkyl, or lower alkyl, then the ring system

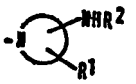
is a ring system of formula II(a) or II(b); (iii) when W is a substituted or unsubstituted 5 or 6 membered heteroaryl radical, and A is a



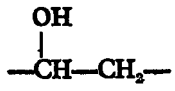
or $—CH_2CH_2—$ radical, and R^1 is hydrogen or lower alkyl, then R^2 is the group —COR wherein R is other than lower alkyl; (iv) when W is a phenyl or a 5 or 6 membered heteroaryl radical, both of which may be substituted or unsubstituted, and A is a



radical, and R^1 is hydrogen, and the ring system

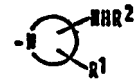


is a ring system of formula II(a), then R^2 is the group —COR wherein R is other than lower alkyl; and (v) when W is substituted or unsubstituted phenyl and A is a



radical, and R^1 is hydrogen or lower alkyl, then R^2 is the group —COR wherein R is other than lower alkyl.

11. Heterocyclic compounds according to claim 10 in which



W, R^1, R^2, R, $X^{\ominus}$, Acyl and the term "lower" have the meanings defined in Claim 10,

and A represents a lower alkylene radical, a mono- or di-keto lower alkylene radical or a hydroxy lower-alkylene radical or a bivalent radical of the formula

$$—NH . CO . CH_2—,$$

$$—NH . CO . CH_2 . CH_2—,$$

$$—N(\text{Acyl}) . CH_2 . C{\equiv}C . CH_2—,$$

$$—O—CH_2 . CH(OH) . CH_2—$$

or

$$—O—(\text{lower-alkylene})—.$$

12. Heterocyclic compounds according to Claim 11, in which

W, R^1, R^2, R, $X^{\ominus}$ Acyl and the term "lower" have the meanings defined in Claim 11, and A represents a lower alkylene radical.

13. Heterocyclic compounds according to Claim 12, in which the lower alkylene radical A is a $—CH_2—$, $—(CH_2)_3—$ or $—(CH_2)_4—$ radical.

14. Heterocyclic compounds according to Claim 12, in which the lower alkylene radical A is a $—(CH_2)_2—$ radical.

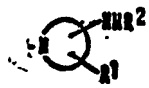
15. Heterocyclic compounds according to Claim 11, in which

W, R^1, R^2, R, X^-, Acyl and the term "lower" have the meanings defined in Claim 11, and A represents a mono-keto lower alkylene radical.

16. Heterocyclic compounds according to Claim 15, in which the mono-keto lower alkylene radical A has the formula $—CO . CH_2—$ or $—CO . (CH_2)_2—$.

17. Heterocyclic compounds according to Claim 15, in which the mono-keto lower alkylene radical A has the formula $—CO—(CH_2)_3—$.

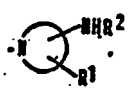
18. Heterocyclic compounds according to Claim 11, in which



W, R^1, R^2, R, $X^{\ominus}$, Acyl and the term "lower" have the meanings defined in Claim 11, and A represents a diketo lower alkylene radical.

19. Heterocyclic compounds according to Claim 18, in which the diketo lower alkylene radical A is a $—CO . CO—$ radical.

20. Heterocyclic compounds according to Claim 11, in which



W, R^1, R^2, R, $X^{\ominus}$, Acyl and the term "lower" have the meanings defined in Claim 11, and A represents a hydroxy lower alkylene radical.

21. Heterocyclic compounds according to Claim 20, in which the hydroxy lower alkylene radical A is a

$$-CH(OH).CH_2-,$$

$$-CH(OH).(CH_2)_2-$$

or

$$-CH(OH).(CH_2)_3-$$

radical.

22. Heterocyclic compounds according to Claim 11, in which

W, R^1, R^2, R, $X^\ominus$, Acyl and the term "lower" have the meanings defined in Claim 11, and A represents a $-NH.CO.CH_2-$ or $-NH.CO.(CH_2)_2-$ radical.

23. Heterocyclic compounds according to any one of Claims 11 to 22, in which W is a phenyl, mono- or di-halophenyl, mono-, di or tri-lower alkoxy-phenyl, mono- or di-lower alkylphenyl, aminophenyl, nitrophenyl, methylenedioxy-phenyl, naphthyl, quinolyl, dihydroxyphenyl, pyridyl, pyrimidyl or pyrrolyl radical.

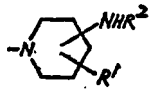
24. Heterocyclic compounds according to Claim 23, in which the group W is a phenyl, chlorophenyl, fluorophenyl, dichlorophenyl, mono-, di- or tri-methoxyphenyl, aminophenyl, nitrophenyl, di-methylphenyl, 1-naphthyl, 2-naphthyl or 2-quinolyl radical.

25. Heterocyclic compounds according to any one of Claims 11 to 24, in which R^1 is hydrogen.

26. Heterocyclic compounds according to any one of Claims 11 to 25, in which R^2 is the benzoyl radical.

27. Heterocyclic compounds according to any one of Claims 11 to 26, in which

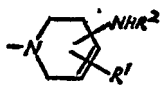
represents a ring system of formula



wherein R^1 and R^2 are as defined in Claim 11.

28. Heterocyclic compounds according to any one of Claims 11 to 26, in which

represents a ring system of formula



wherein R^1 and R^2 are as defined in Claim 11.

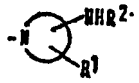
29. Heterocyclic compounds according to Claim 10, in which

W, R^1, R^2, R, $X^\ominus$, Acyl and the term "lower" have the meaning defined in Claim 10 and A is a —NH . CO . $(CH_2)_3$— radical.

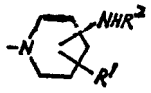
30. Heterocyclic compounds according to Claim 29, in which W is a phenyl radical.

31. Heterocyclic compounds according to Claim 29 or 30, in which R^2 is —COR wherein R is phenyl.

32. Heterocyclic compounds according to any one of Claims 29, 30 or 31, in which R^1 is hydrogen and



represents a ring system of formula

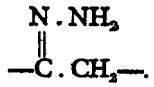


wherein R^2 is as defined in Claim 10.

33. Heterocyclic compounds according to Claim 10, in which

W, R^1, R^2, R, $X^\ominus$, Acyl and the term "lower" have the meanings defined in Claim 10 and A is the oxime, aminoguanidone or substituted or unsubstituted hydrazone derivative of a mono- or di-keto lower alkylene radical.

34. Heterocyclic compounds according to Claim 33, in which the derivative A has the formula

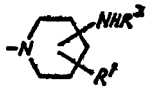


35. Heterocyclic compounds according to Claim 33 or 34, in which W is a dichlorophenyl radical.

36. Heterocyclic compounds according to any one of Claims 33, 34 or 35, in which R^2 is —COR wherein R is phenyl.

37. Heterocyclic compounds according to any one of Claims 33 to 36, in which R^1 is hydrogen and

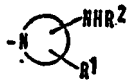
represents a ring system of formula



wherein R^2 is as defined in Claim 10.

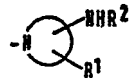
38. 1-[2-(3,4-Methylenedioxyphenyl)ethyl]-4-benzamidopiperidine.
39. 1-[2-(*o*-Chlorophenyl)ethyl]-4-benzamidopiperidine.
40. 1-[2-(2-Naphthyloxy)ethyl]-4-benzamidopiperidine.
41. 1-[2-(Cyclohexyl)ethyl]-4-benzamidopiperidine.
42. 1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-acetamidopyridinium iodide.
43. 1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-acetamidopiperidine.
44. 1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-aminopiperidine.
45. 1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-benzamidopiperidine.
46. 1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-(2-chlorobenzamido)piperidine.
47. 1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-piperonyloylaminopiperidine.
48. 1-[2-(3,4,5-Trimethoxyphenyl)ethyl]-4-benzamidopiperidine.
49. 1-[2-(3,4-Dihydroxyphenyl)ethyl]-4-benzamidopiperidine.
50. 1-Phenacyl-4-benzamidopiperidine.
51. 1-[2-(3,4-Dihydroxyphenyl)-2-oxoethyl]-4-benzamidopiperidine.
52. 1-[2-(1-Naphthyl)ethyl]-4-benzamidopiperidine.
53. 1-[2-(2-Naphthylethyl]-4-benzamidopiperidine.
54. 1-[2-(3-Indenyl)ethyl]-4-benzamidopiperidine.
55. 1-[3-(3-Indenyl)propyl]-4-benzamidopiperidine.
56. 1-[2-(4-Pyridyl)ethyl]-4-benzamidopiperidine.
57. 1-[2-(4-Pyrimidinyl)ethyl]-4-benzamidopiperidine.
58. 1-[2-(4-Imidazolyl)ethyl]-4-benzamidopiperidine.
59. 1-(2-Pyrrolyl-oxalyl)-4-benzamidopiperidine.
60. 1-[2-Hydroxy-2-(2-pyrrolyl)ethyl]-4-benzamidopiperidine.
61. 1-[3-(1-Phenyl-5-methylpyrazol-4-yl)-3-oxo-propyl]-4-benzamido-piperidine.
62. 1-[2-(3-Benzo[b]thienyl)ethyl]-4-benzamidopiperidine.
63. 1-[2-(2-Quinolyl)ethyl]-4-benzamidopiperidine.
64. 1 - [N - (5 - Ethoxycarbonyl - 4 - phenylthiazol - 2 - yl)carbamoylmethyl] - 4 - benzamidopiperidine.
65. 1 - [N - (2 - Methylphenyl)carbamoylethyl] - 4 - benzamidopiperidine.
66. 1 - [4 - (N - Propionyl - N - [2,6 - dichlorophenyl]amino but - 2 - yn - 1 - yl] - 4 - benzamidopiperidine.
67. 1-[1-(4-Acetamidophenoxy)-2-hydroxyprop-3-yl]-4-benzamidopiperidine.
68. 1-(5-Acetamido-2-hydroxybenzyl)-4-benzamidopiperidine.
69. 1-[4-(4-Fluorophenyl)-4-oxobutyl]-4-benzamidopiperidine.
70. 1-[2-(3-Benz[g]indolyl)ethyl]-4-benzamidopiperidine.
71. 1-[2-(2-Pyridyl)ethyl]-4-benzamidopiperidine.
72. 1-(2-Hydroxy-2-phenylethyl)-4-benzamidopiperidine.
73. 1-[2-(5-Phenylthien-2-yl)ethyl]-4-benzamidopiperidine.
74. 1-[2-(2-Benzimidazolyl)ethyl)-4-benzamidopiperidine.
75. 1-[3-(1-Naphthoxy)-2-hydroxyprop-1-yl]-4-benzamidopiperidine.
76. 1-[2-(*p*-Nitrophenyl)ethyl]-4-benzamidopiperidine.
77. 1-[2-(*p*-Aminophenyl)ethyl]-4-benzamidopiperidine.
78. 1-[2-(*p*-Acetamidophenyl)ethyl]-4-benzamidopiperidine.
79. 1-[2-Phenethyl]-4-benzamidopyridinium bromide.
80. 1-Phenethyl-4-benzamido-1,2,5,6-tetrahydropyridine.
81. 1-[2-(4-[*p*-Chlorophenyl]-2-phenylthiazol-5-yl)ethyl]-4-benzamido-piperidine.
82. 1-[2-(*p*-Chlorophenyl)thiazol-4-yl]methyl-4-benzamidopiperidine.
83. 1-[2-(*p*-Chlorophenyl)ethyl]-4-benzamidopiperidine.
84. 1-[2-(2,6-Dichlorophenyl)ethyl]-4-benzamidopiperidine.
85. 1-(3-Phenylprop-2-yl)-4-benzamidopiperidine.
86. 1-[2-(*o*-Nitrophenyl)ethyl]-4-benzamidopiperidine.
87. 1-[(3,4-Dichlorobenzoyl)methyl]-4-benzamidopiperidine.
88. 1-[2-(*o*-Aminophenyl)ethyl]-4-benzamidopiperidine.
89. 1-[2-(3,4-Dichlorophenyl)-2-hydroxyethyl]-4-benzamidopiperidine.
90. 1-[2-(3,4-Dichlorophenyl)-2-hydrazonoethyl]-4-benzamidopiperidine.
91. 1-[2-(3,4-Dichlorophenyl)ethyl]-4-benzamidopiperidine.
92. 1-(3-Phenylpropyl)-4-benzamidopiperidine.
93. 1-[4-(*p*-Fluorophenyl)-n-butyl]-4-benzamidopiperidine.
94. 1-[2-(3,4-Dimethylphenyl)ethyl]-4-benzamidopiperidine.
95. 1-[4-(*p*-Fluorophenyl)-4-oxobutyl]-4-benzamidopiperidine hydrochloride.
96. 1-(4-Phenyl-4-oxobutyl)-4-benzamidopiperidine.
97. 1-[4-(2,5-Dimethylphenyl)-4-oxobutyl]-4-benzamidopiperidine.
98. 1-[4-(2,4-Dimethylphenyl)-4-oxobutyl]-4-benzamidopiperidine.
99. 1-(4-Phenylbutyl)-4-benzamidopiperidine.
100. 1-(3,4-Methylenedioxybenzyl)-4-benzamidopiperidine.

101. 1-[2-(*p*-Methoxyphenyl)ethyl]-4-benzamidopiperidine.
102. N-Phenyl-4-(4-benzamidopiperid-1-yl)butyramide.
103. 2-(4-Benzamidopiperid-1-yl)methylbenzo-1,4-dioxan.
104. 1-[4-(*p*-Chlorophenyl)-4-oxobutyl]-4-benzamidopiperidine.
105. 1-(2-Phenoxyethyl)-4-benzamidopiperidine.
106. 1-(4-Phenyl-4-hydroxybutyl)-4-benzamidopiperidine.
107. 1-[4-(*p*-Fluorophenyl)-4-hydroxybutyl]-4-benzamidopiperidine.
108. 1-[3-(1-Naphthyloxy)propyl]-4-benzamidopiperidine.
109. 1-[2-(1,2,3,4-Tetrahydro-6-naphthyl)-2-oxoethyl]-4-benzamido-piperidine.
110. 1 - [2 - (1,2,3,4 - Tetrahydro - 6 - naphthyl) - 2 - hydroxyethyl] - 4 - benzamidopiperidine.
111. 1 - [4 - (1,2,3,4 - Tetrahydro - 6 - naphthyl) - 4 - oxobutyl] - 4 - benzamidopiperidine.
112. The acid addition and quaternary ammonium salts of the compounds according to any one of Claims 41, 43 to 78 and 80 to 85.
113. The acid addition and quaternary ammonium salts of the compounds according to any one of Claims 86 to 94 and 96 to 111.
114. A pharmaceutical composition according to Claim 1, which comprises a heterocyclic compound according to any one of Claims 11 to 31 wherein W, A, R^1, Acyl and the term "lower" are as defined in any one of Claims 11 to 31; the ring system



is a ring system of formula II(b) or II(c) as shown in Claim 10; and R^2 is the group —COR wherein R is a substituted or unsubstituted aryl radical (including heteroaryl radicals), aryl-lower-alkyl, diaryl-lower-alkyl, cycloalkyl containing five to seven ring carbon atoms or lower alkyl radical; or according to any one of Claims 41, 43, 45 to 78, 80 to 85 and 112.
115. A pharmaceutical composition according to Claim 1, which comprises a heterocyclic compound according to any one of Claims 10, and 32 to 40, wherein n, W, A, R^1, Acyl and the term "lower" are as defined in any one of Claims 10 and 32 to 40; the ring system

is a ring system of formula II(b) or II(c) as shown in Claim 10; and R^2 is the group —COR wherein R is a substituted or unsubstituted aryl radical (including heteroaryl radicals), aryl-lower-alkyl, diaryl-lower-alkyl, cycloalkyl containing five to seven ring carbon atoms or lower alkyl radical; or according to any one of Claims 86 to 111 and 113.
116. A process for the preparation of a compound of formula (I) as claimed in Claim 11 wherein



W, R^1, R, $X^{\ominus}$, A, Acyl and the term "lower" have the meanings defined in Claim 11 and R^2 is the —COR group, in which process a compound of general formula

III(a) III(b) III(c)

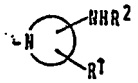
is reacted with an alkylating or acylating agent of the general formula

$$[W]—A—Y \qquad (IV)$$

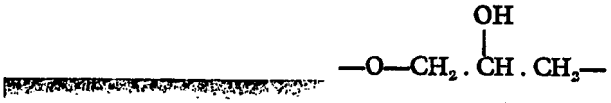
(in which formulae W, R^1, R, and A have the meanings defined above and Y is a halogen atom or an equivalent replaceable atom or radical.

117. A process according to Claim 116, in which Y is a halogen atom selected from chlorine and bromine.

118. A process for the preparation of a compound of formula (I) as claimed in Claim 11 wherein



represents a ring system of formula II(b) or II(c) as shown in Claim 10, R^2 is the —COR group, W,R,R^1 and the term "lower" have the meaning defined in Claim 11, and A is a hydroxy-lower alkylene or



radical, in which process a compound of formula

$$[W—]—A^1—H \qquad (V)$$

(in which W has the meaning defined above and A^1 is an epoxy-substituted lower alkylene radical or a

radical) is reacted with a compound of formula III(b) or III(c) as shown in Claim 116 wherein R^1 and R are as hereinabove defined.

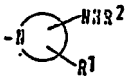
119. A process for the preparation of a compound of formula (I) as claimed in Claim 11 wherein

represents a ring system of formula II(b) or II(c) as shown in Claim 10, R^2 is the —COR group, W,R,R^1 and the term "lower" have the meanings defined in Claim 11 and A is a lower alkylene radical, in which process a compound of formula

$$[W—]—B \qquad (VII)$$

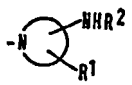
(wherein W has the meaning defined above and B is a straight or branched chain alkenyl residue) is reacted with a compound of formula III(b) or III(c) as shown in Claim 116 wherein R and R^1 are as hereinabove defined.

120. A process for the preparation of a compound of formula (I) as claimed in Claim 11 wherein



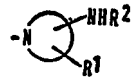
represents a ring system of formula II(a) or II(c) as shown in Claim 10, and

W, R, R^1, $X^\ominus$, A, Acyl and the term "lower" have the meanings defined in Claim 11 and R^2 is the —COR group, in which process a compound of general formula (I) in which



W, R^1, $X^\ominus$, A, Acyl and the term "lower" have the meanings defined above and R^2 is a hydrogen atom, is acylated with either (i) a reactive derivative of an acid of general formula R . COOH (wherein R is aryl, heteroaryl, aryl-lower-alkyl, diaryl-lower-alkyl, cycloalkyl or lower alkyl), or (ii) a haloester of formula Hal . CO . R (wherein Hal is a halogen atom and R is lower alkoxy, aryloxy or aryl-lower-alkoxy).

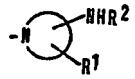
121. A process for the preparation of a compound of formula (I) as claimed in Claim 11 wherein



is a ring system of formula II(a) or II(c) as shown in Claim 10, and W, R^1, $X^\ominus$, A, Acyl and the term "lower" have the meanings defined in Claim 11 and R^2 is the —COR group wherein R is as as defined in connection with formula R . COOH in Claim 120 in which process an acid of formula R . COOH wherein R is as hereinabove defined is reacted with a compound of general formula (I) in which

W, R^1, $X^\ominus$, A, Acyl and the term "lower" have the meanings defined above and R^2 is hydrogen (i) in the presence of a known condensing agent, or (ii) by first activating the amino function of the compound of general formula (I) by known methods.

122. A process for the preparation of a compound of formula (I) as claimed in Claim 11, wherein W, R, R^1, Acyl and the term "lower" have the meanings defined in Claim 11,



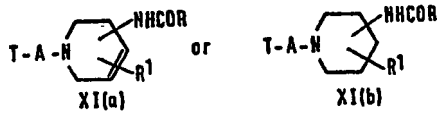
represents a ring system of formula II(b) or II(c) as shown in Claim 10, R^2 is the —COR group, and A is a lower alkylene or a mono- or di-keto lower alkylene radical or a bivalent radical of the formula

$$\begin{array}{l} \text{—N . CH}_2\text{ . C}\equiv\text{C . CH}_2\text{—,} \\ \quad\;\; | \\ \quad\;\; \text{Acyl} \end{array}$$

which process comprises a Mannich reaction using a compound of formula III(b) or III(c) as shown in Claim 116 wherein R^1 and R are as hereinabove defined, as secondary amine, formaldehyde and a suitable reactive derivative of the radical W in which the chain A has been partially formed, and which partially formed chain contains a site of the type known to participate in the Mannich reaction.

123. A process for the preparation of a compound of general formula (I) as claimed in Claim 11, wherein

represents a ring system of formula II(b) or II(c) as shown in Claim 10, R^2 is the —COR group, and W, R, R^1, A, Acyl and the term "lower" have the meanings defined in Claim 11, in which process a compound of formula

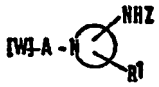


XI(a) XI(b)

(wherein A, R^1 and R have the meanings defined above and T is a known precursor group of W), is reacted with another molecule of the type known in the literature for the conversion of the precursor group T to W.

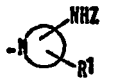
124. A process for the preparation of a compound of general formula (I) as claimed in Claim 11, wherein

is a ring system of formula II(a) or II(c) as shown in Claim 10, and W, R^1, $X^{\ominus}$, A, Acyl and the term "lower" have the meanings defined in Claim 11 and R^2 is a hydrogen atom, in which process a corresponding compound of formula

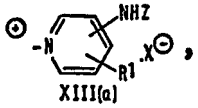


(XII)

(wherein W, A, and R^1 have the meanings defined above,

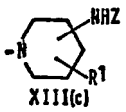


represents a ring system of formula



XIII(a)

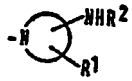
or



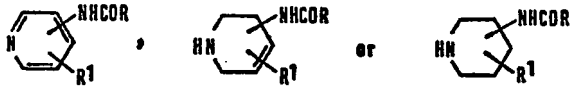
XIII(c)

and Z is a protecting group known in the art for the protection of the amino function) is subjected to a reaction known in the art for the removal of the protecting group.

125. A process for the preparation of a compound of formula (I) as claimed in Claim 10, wherein



W, R^1, R, $X^{\ominus}$, Acyl and the term "lower" have the meanings defined in Claim 10, R^2 is the —COR group and A is a bivalent radical of formula —NH . CO . $(CH_2)_3$—, in which process a compound of general formula



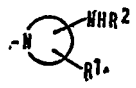
III(a) III(b) III(c)

wherein R and R^1 are as defined in Claim 10, is reacted with an alkylating or acylating agent of the general formula

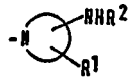
$$[W—]—A—Y \qquad \text{(IV)}$$

(wherein W and A have the meanings defined immediately above and Y is a halogen atom or an equivalent replaceable atom or radical.

126. A process for the preparation of a compound of formula (I) as claimed in Claim 10, wherein



is a ring system of formula II(a) or II(c) as shown in Claim 10, and W, R, R^1, $X^\ominus$, Acyl and the term "lower" have the meanings defined in Claim 10, R^2 is the —COR group and A is the bivalent radical of formula —NH . CO . $(CH_2)_3$—, in which process a compound of general formula (I) in which



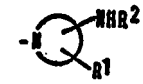
W, R^1, $X^\ominus$, A, Acyl and the term "lower" have the meanings defined immediately above and R^2 is a hydrogen atom, is acylated with either (i) a reactive derivative of an acid of general formula R . COOH (wherein R is aryl, heteroaryl, aryl-lower-alkyl, diaryl-lower-alkyl, cycloalkyl or lower alkyl), or (ii) a haloester of formula Hal . CO . R (wherein Hal is a halogen atom and R is lower alkoxy, aryloxy or aryl-lower-alkoxy).

127. A process for the preparation of a compound of formula (I) as claimed in Claim 10 wherein

is a ring system of formula II(a) or II(c) as shown in Claim 10, and W, R^1, $X^\ominus$, Acyl and the term "lower" have the meanings defined in Claim 10, R^2 is the —COR group, wherein R is as defined in connection with formula R . COOH in Claim 126, and A is the bivalent radical —NH . CO . $(CH_2)_3$— in which process an acid of formula R . COOH, wherein R is as hereinbefore defined, is reacted with a compound of general formula (I) in which

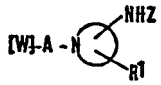
W, R^1, $X^\ominus$, A, Acyl and the term "lower" have the meanings defined immediately above and R^2 is hydrogen (i) in the presence of a known condensing agent or (ii) by first activating the amino function of the compound of general formula (I) by known methods.

128. A process for the preparation of a compound of general formula (I) as claimed in Claim 10, wherein



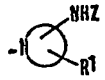
is a ring system of formula II(a) or II(c) as shown in Claim 10, and W, R^1, $X^\ominus$, Acyl and the term "lower" have the meanings defined in Claim 10, R^2 is a hydrogen atom

and A is the bivalent radical —NH . CO . $(CH_2)_3$—, in which process a corresponding compound of formula

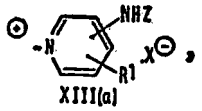


(XII)

(wherein W, A and R^1 have the meanings defined immediately above,

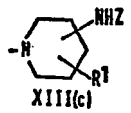


represents a ring system of formula



XIII(a)

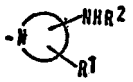
or



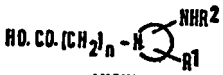
XIII(c)

wherein R^1 and $X^{\ominus}$ are as defined in Claim 10 and Z is a protecting group known in the art for the protection of the amino function) is subjected to a reaction known in the art for the removal of the protecting group.

129. A process for the preparation of compounds of general formula (I) as claimed in Claim 10, wherein



represents a ring system of formula II(b) or II(c) as shown in Claim 10, and W, R^1, R^2, R, $X^{\ominus}$, and the term "lower" have the meanings defined in Claim 10 and A is a bivalent radical of the formula —NH . CO . $(CH_2)_n$— wherein n is 1, 2 or 3, in which process a reactive derivative of an acid of formula



(XIV)

is reacted with a primary amine of formula

$$[W—]—NH_2 \qquad (XV)$$

(in which formulae

W, R^1, R^2, R, $X^{\ominus}$, n and the term "lower" have the meanings defined immediately above).

130. A process for the preparation of compounds of general formula (I) as claimed in Claim 10, wherein

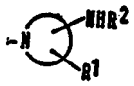
represents a ring system of general formula II(b) or II(c) as shown in Claim 10, R^2

is the —COR group wherein R is as defined in Claim 10, A is a lower alkylene radical or the bivalent radical —NH . CO . $(CH_2)_n$— wherein n is 1, 2 or 3, and W, "lower" and R^1 have the meanings defined in Claim 10, in which process a compound of the general formula

[W—]—A—OH (XVI)

(in which W and A have the meanings defined immediately above) is reacted with a compound of the general formula III(b) or III(c) as shown in Claim 125 wherein R and R^1 are as hereinabove defined.

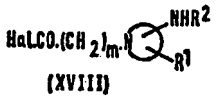
131. A process for the preparation of compounds of general formula (I) as claimed in Claim 10, wherein



represents a ring system of formula II(b) or II(c) as shown in Claim 10, W and R^1 have the meanings defined in Claim 10, R^2 is the —COR group wherein R has the meanings defined in Claim 10 and A is a mono-keto lower alkylene radical of formula —CO . $(CH_2)_m$— in which m is 1 to 5, in which process a compound of formula

[W—]—H (XVII)

is acylated with an acid halide of formula

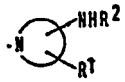


(XVIII)

(wherein W,

R^1, R^2, R and m have the meanings defined immediately above and Hal is a halogen atom).

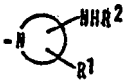
132. A process according to any one of Claims 116, 117, 120, 121 and 124, in which a compound of formula (I) is produced in which



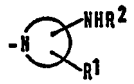
represents a ring system of formula II(a) as defined in Claim 10, and this compound is reduced to the corresponding compound in which

represents a ring system of formula II(b) or II(c) as defined in Claim 10.

133. A process according to any one of Claims 125 to 128, in which a compound of formula (I) is produced in which



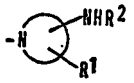
represents a ring system of formula II(a) as defined in Claim 10, and this compound is reduced to the corresponding compound in which



represents a ring system of formula II(b) or II(c) as defined in Claim 10.

134. A process according to any one of Claims 116, 117 and 132, in which a compound of formula (I) is produced in which

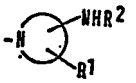
represents a ring system of formula II(b) as defined in Claim 10, and this compound is reduced to the corresponding compound in which



represents a ring system of formula II(c) as defined in Claim 10.

135. A process according to any one of Claims 125, 129 to 131 and 133 in which a compound of formula (I) is produced in which

represents a ring system of formula II(b) as defined in Claim 10, and this compound is reduced to the corresponding compound in which



represents a ring system of formula II(c) as defined in Claim 10.

136. A process according to any one of Claims 116, 117, 120 to 124, 132 and 134, in which a compound of formula (I) is produced in which A is a mono- or-diketo lower alkylene radical, and this compound is reduced to one in which A contains one or two hydroxyl groups.

137. A process according to any one of Claims 116, 117, 120 to 124 and 132, in which a compound of formula (I) is produced in which A is a mono- or di-keto lower alkylene radical and this compound is reduced to one in which the keto group/groups has/have been replaced by one or two methylene groups.

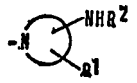
138. A process according to any one of Claims 116, 117, 120 to 124, 131, 132 and 134, in which a compound of formula (I) is produced in which A is a mono- or di-keto lower alkylene radical, and this compound is converted into the substituted or unsubstituted hydrazone, oxime or aminoguanidone derivative thereof.

139. A process according to any one of Claims 116 to 123, or any one of Claims 132, 134, 136 and 137 all as dependent on any one of Claims 116, 117, 120 and 121, in which a compound of formula (I) is produced in which

is a ring system of formula II(a) or II(c) as shown in Claim 10 and R^2 is the —COR

group, and this compound is hydrolysed to the corresponding compound of formula (I) in which R^2 is hydrogen, which in turn may be further reacted to give a compound of formula (I) in which R^2 is a different —COR group.

140. A process according to any one of Claims 125 to 127, 129, 130, and 131, or any one of Claims 133 and 135 both as dependent on any one of Claims 125 to 127 and 129, in which a compound of formula (I) is produced in which



is a ring system of formula II(a) or II(c) as shown in Claim 10 and R^2 is the —COR group, and this compound is hydrolysed to the corresponding compound of formula (I) in which R^2 is hydrogen, which in turn may be further reacted to give a compound of formula (I) in which R^2 is a different —COR group.

141. A process according to any one of Claims 116 to 124, 132, 134, 136, 137 and 139, in which a compound of formula (I) is produced in which the radical W is substituted by one or more methoxy groups, and this compound is hydrolysed to the corresponding compound containing one or more hydroxyl groups.

142. A process according to any one of Claims 125 to 131, 133, 135 and 140, in which a compound of formula (I) is produced in which the radical W is substituted by one or more methoxy groups, and this compound is hydrolysed to the corresponding compound containing one or more hydroxyl groups.

143. A process according to any one of Claims 116 to 124, 132, 134, 136, 137, 139 and 141 in which a compound of formula (I) is produced in which the radical W is substituted by a nitro group, and this compound is reduced to the corresponding amino compound, which in turn may be further alkylated or acylated.

144. A process according to any one of Claims 125 to 131, 133, 135, 140 and 142, in which a compound of formula (I) is produced in which the radical W is substituted by a nitro group, and this compound is reduced to the corresponding amino compound, which in turn may be further alkylated or acylated.

145. A process according to any one of Claims 116, 117, 119 to 124, 132, 134, 137, 139, 141 and 143, in which A in the compound produced is a lower alkylene radical.

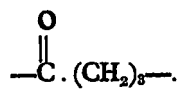
146. A process according to Claim 145, in which the lower alkylene radical is an ethylene radical.

147. A process according to Claim 130, or any one of Claims 140, 142 and 144 all as dependent on Claim 130, in which A in the compound produced is a lower alkylene radical.

148. A process according to Claim 147, in which the lower alkylene radical is an ethylene radical.

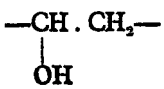
149. A process according to any one of Claims 116, 117, and 120 to 124, or any one of Claims 139, 141 and 143 all as dependent on any one of Claims 116, 117, and 120 to 123, in which A in the compound produced is a mono- or di-keto lower alkylene radical.

150. A process according to Claim 149, in which A is a mono-keto lower alkylene radical of formula



151. A process according to any one of Claims 116 to 118, 120, 121, 123, 124, 132, 134 and 136 or any one of Claims 139, 141 and 143 all as dependent on any one of Claims 116 to 118, 120, 121, 123, 124, 132, 134 and 136, in which A in the compound produced is a hydroxy lower alkylene radical.

152. A process according to Claim 151, in which the hydroxy lower alkylene radical has the formula



or

$$-CH(OH).(CH_2)_3-.$$

153. A process according to any one of Claims 116, 117, 120, 121, 123, 124, 132 and 134, or any one of Claims 139, 141 and 143 all as dependent on any one of Claims 116, 117, 120, 121, 123, 124, 132 and 134, in which A in the compound produced is an —O—(lower alkylene)— radical.

154. A process according to Claim 153, in which the —O—(lower alkylene)— radical is of formula $-O.(CH_2)_2-$ or $-O-(CH_2)_3-$.

155. A process according to any one of Claims 116, 117, 120, 121, 123, 124, 132 and 134, or any one of Claims 139, 141 and 143 all as dependent on any one of Claims 116, 117, 120, 121, 123, 124, 132 and 134, in which A in the compound prepared is of formula $-NH.CO.CH_2-$ or $-NH.CO.(CH_2)_2-$.

156. A process according to any one of Claims 125 to 128, or Claim 133 as dependent on any one of Claims 125 to 128, or any one of Claims 135, 140, 142 and 144 all as dependent on any one of Claims 125 to 127, in which A in the compound prepared is of formula $-NH.CO.(CH_2)_3-$.

157. A process according to Claims 129 or 130, in which A in the compound prepared is of formula $-NH.CO.(CH_2)_n-$ wherein n is 1, 2 or 3.

158. A process according to any one of Claims 116 to 123, or any one of Claims 132, 134, 136, 137, 139, 141, 143, 145, 146 and 149 to 155 all as dependent on any one of Claims 116, 117, and 120 to 123, in which R^2 in the compound prepared is the —COR group wherein R is as defined in Claim 10.

159. A process according to Claim 158, in which the —COR group is the benzoyl group.

160. A process according to any one of Claims 125 to 127, 129, 130, 131, 138, 147, 148 and 157, or any one of Claims 133, 135, 140, 142, 144, and 156 all as dependent on any one of Claims 125 to 127 and 129, in which R^2 in the compound prepared is the —COR group wherein R is as defined in Claim 10.

161. A process according to Claim 160, in which the —COR group is the benzoyl group.

162. A process according to any one of Claims 116 to 124, 132, 134, 136, 137, 139, 141, 143, 145, 146, 149, 155, 158 and 159, in which W in the compound prepared is a phenyl, mono- or di-halophenyl, mono-, di- or tri-lower alkoxy-phenyl, mono- or di-hydroxyphenyl, naphthyl, pyridyl, pyrimidinyl, quinolyl, mono- or di-lower alkylphenyl, benz[g]indolyl, nitrophenyl, aminophenyl acylaminophenyl or methylendioxyphenyl radical.

163. A process according to Claim 162, in which W is a phenyl, chloro-, bromo- or fluoro-phenyl, dichlorophenyl, methylphenyl, dimethylphenyl, mono-, di- or trimethoxyphenyl naphth-1-yl, naphth-2-yl or quinol-2-yl radical.

164. A process according to any one of Claims 125 to 131, 133, 135, 138, 140, 142, 144, 147, 148, 156, 157, 160 and 161, in which W in the compound prepared is a phenyl, mono- or di-halophenyl, mono-, di- or tri-lower alkoxyphenyl, mono- or dihydroxyphenyl, naphthyl, pyrridyl, pyrimodinyl, quinolyl, mono- or di-lower alkylphenyl, benz[g]indolyl, nitrophenyl, aminophenyl, acylaminophenyl methylenedioxy phenyl, benzo-1,4-dioxanyl, or tetrahydroxaphthyl radical.

165. A process according to Claim 164, in which W is a phenyl, chloro-, bromo- or fluoro-phenyl, dichlorophenyl, methylphenyl, dimethylphenyl, mono-, di- or trimethoxyphenyl, naphth-1-yl, naphth-2-yl or quinol-2-yl radical.

166. A process according to any one of Claims 116 to 124, 132, 134, 136, 137, 139, 141, 143, 145, 146, 149 to 155, 158, 159, 162 and 163, in which R^1 in the compound prepared is hydrogen.

167. A process according to any one of Claims 125 to 131, 135, 138, 140, 142, 144, 147, 148, 156, 157, 160, 161, 164 and 165, in which R^1 in the compound prepared is hydrogen.

168. A process according to any one of Claims 116 to 124, 132, 134, 136, 137, 139, 141, 143, 145, 146, 149, 155, 158, 159, 162, 163 and 166 substantially as described herein and shown with reference to any of Examples 1 to 43.

169. A process according to any one of Claims 125 to 131, 133, 135, 138, 140, 142, 144, 147, 148, 156, 157, 160, 161, 164, 165 and 167, substantially as described herein and shown with reference to any of Examples 50 to 77 and 80.

170. Heterocyclic compounds according to Claim 11 when prepared by the pro-

cess claimed in any of Claims 116 to 124, 132, 134, 136, 137, 139, 141, 143, 145, 146, 149, 155, 158, 159, 162, 163, 166, and 168.

171. Heterocyclic compounds according to Claim 10 when prepared by the process claimed in any of Claims 125 to 131, 133, 135, 138, 140, 142, 144, 147, 148, 156, 157, 160, 161, 164, 165, 167, and 169.

172. Compounds according to Claim 11 substantially as described herein and shown with reference to any one of Examples 1 to 43.

173. Compounds according to Claim 10 substantially as described herein and shown with reference to any one of Examples 50 to 77 and 80.

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